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THE CHOROID PLEXUSES OF THE LATERAL VENTRICLES OF THE BRAIN, THEIR HISTOLOGY, NORMAL AND PATHOLOGICAL, (IN RELATION SPECIALLY TO INSANITY).

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WHILE much work has been done of late on the normal and pathological histology of the membranes and vessels of the brain, there has been practically nothing written for the last quarter of a century on the choroid plexuses themselves, with the exception in 1886 of Albarran's "Sur la structure d'un renflement situé au niveau du bord libre des plexus choroïdes des ventricules lateraux." It was, therefore, suggested to me, while acting as pathologist to the Crichton Royal Institution, Dumfries, that a research into the normal histology of this structure could not fail to be both interesting and profitable; and that in all probability there were important alterations to be found in the plexuses of the insane, analogous to those changes, described by Robertson and others, in the vessels and tissue elements of the pia-arachnoid of the brain. How far this has been borne out, the conclusions arrived at in the course of the investigation must show. These conclusions, I may state, are based upon the microscopic study of the choroid plexuses in sixty-five cases. Six of these, from general hospital cases, were kindly supplied to me by Dr. Sutherland, of the Western Infirmary, Glasgow. Forty-nine of the plexuses

from the insane were given me by Dr. W. Ford Robertson, Pathologist to the Laboratory of the Scottish Asylums, Edinburgh, to whom I am also indebted for much valuable help. The remainder were from cases examined by myself at the Crichton Royal Institution. For the study of the normal structure I also made preparations from several absolutely fresh choroid plexuses of the sheep, ox and calf. I desire to express my thanks to Dr. J. Rutherford for placing unlimited time at my disposal during the progress of this research, and generally facilitating the work in every way he could. My thanks are likewise due to Dr. James Finlayson, Honorary Librarian to the Faculty of Physicians and Surgeons, Glasgow, to whom I am much indebted for the assistance he gave me in obtaining references in literature to the subject under discussion.

Normal Histology of the Choroid Plexus.

It is generally accepted that the choroid plexus is formed of pia mater, while it is held that the velum interpositum is composed of two layers of pia mater, between which are contained arachnoidal tissue and blood vessels.[1*]

As the choroid plexuses are only fringes of the velum interpositum, one would expect to find arachnoidal tissue here also, but such is not described, the generally accepted view being that they are composed of pia mater alone.

Lately, however, W. F. Robertson and Middlemass[2] have formulated the doctrine that in the soft coverings of the brain two distinct membranes do not exist. They hold that there is essentially only one structure throughout, and therefore only one membrane, which they propose to call pia-arachnoid. By means of horizontal sections Robertson has demonstrated that the so-called sub-arachnoid spaces may be seen in miniature from immediately under the endothelial covering on the outer surface right down to the inner surface just external to the cortical tissues.

To my mind, after an examination of Dr. Robertson's

* The numbers refer to bibliography at end of paper.

sections, this contention of the oneness of structure of the pia mater and arachnoid has been proved, and it seems to me that the basis of the choroid plexus consists essentially of the same structure as the pia-arachnoid covering the surface of the brain, and likewise resembles a "spongy lymph sac."

The basis of the choroid plexus is delicate white fibrous tissue. The white fibres are gathered together into bundles or trabeculæ of varying thickness and length. These bundles interlace with and cross over one another, after the manner of a network, forming numerous spaces of all shapes. These spaces, inaccurately placed above and alongside of one another, form freely communicating cavities containing fluid, and are lined throughout by a single layer of flattened endothelial cells with large oval nuclei. The meshes of these networks are larger and smaller, the largest being quite microscopic in size, and the smallest showing only a solitary endothelial cell.

In the pia-arachnoid itself these spaces are largest in the centre of the membrane, where they form the so-called "subarachnoid spaces," or about the base of the brain the "arachnoid cisterns."

Much the same condition may be seen in the more central parts of the glomus—a fusiform swelling of the plexus seen at the junction of the body with the descending horn of the lateral ventricle—where these cavities often attain a considerable size. This might be taken as evidence that the choroid plexus consists of two distinct structures, viz., an external layer of pia mater and a central mass of arachnoidal tissue. Such, however, I cannot believe. It seems to me that, as in the case of the pia-arachnoid on the surface of the brain, there is only one structure throughout. Most marked in the centre of the glomus, the lymph spaces get smaller and smaller as we pass towards the surface, till it becomes difficult to make them out. But even here in many cases it is possible to do so, and at most these relatively dense portions of the plexus are but loose areolar tissue lying alongside distinct and easily recognised sinuses.

The choroid plexus, then, may be said to be composed of a duplication of the external pia-arachnoid, since the basis of the plexus resembles it in every way.

There is also a small quantity of elastic tissue in the form of fine threads or filaments. These elastic filaments may be seen lying longitudinally on the surface of a connective tissue bundle, and also winding round and encircling it with several spiral turns. This is brought out by treating a portion of teased choroid plexus with acetic acid. The connective tissue trabeculæ then swell up, and show circular or spiral markings with a distinct dark thread at the point of constriction. A continuous spiral may be traced here and there around the bundle, but the appearance of separate rings is more commonly observed.

This arrangement of the elastic fibres in areolar tissue was first pointed out by Henle: where only separate rings are observed, it has been suggested by Schäfer that this reaction is not due to the presence of elastic fibres, but that "the bundles in question are naturally invested with a delicate sheath, which, like elastic tissue, resists acetic acid, but, on the swelling up of the bundle under the operation of that agent, is rent into shreds or segments, mostly annular or spiral, which cause the constrictions. In other cases the union of branches of the cells around a bundle may be the cause of the appearance."[3]

Connective tissue cells are also found on the surface of the bundles or lying between them, and most frequently assume the spindle or branching form. Pigmented cells may here and there be seen, but their number is never large.

Vessels of the Choroid Plexus.

The choroid plexus is a very vascular structure and its vessels are exceedingly tortuous. The large choroidal vein and the principal arteries run longitudinally along its base. The branches of the latter pass mainly upwards and go on dividing till eventually a very close capillary network is formed.

Arteries.—The larger arteries contain several layers of

muscular tissue, and a well marked adventitial coat composed of wavy connective tissue fibres running parallel to the course of the vessel. Outside this adventitial coat, and flattened along it, are the lymph spaces of the pia-arachnoid; indeed, the connective tissues of the two structures gradually merge into one another. The elastic lamina, too, seems to be well developed in these arteries.

Before describing the arterioles as normally met with in the choroid plexus, let me quote from W. F. Robertson's description of them as found in the pia-arachnoid of the brain:

"There is a fact regarding the arterioles of the pia-arachnoid that, I think, helps us to understand the true constitution of the membrane. It is that they have no proper adventitial coat. Immediately outside of the muscular wall there is a single layer of endothelium which is continued down to the capillaries as pointed out by Klein. Obersteiner believes that this layer forms the outer wall of a lymph sac, a point that must be regarded, I think, as doubtful. Beyond this endothelial layer lying on the muscular coat, the vessels, with the exception of some of the very largest of them, have no special investment of longitudinally disposed fibrous tissue, such as is found in the vessels elsewhere. They are, as it were, naked vessels surrounded by trabeculæ and lymph spaces. The trabecular tissue, however, practically forms for them a common adventitia. From a consideration of these features of structure Dr. Middlemass and I have advocated the view that the whole extra-vascular structure of the soft membranes may be looked upon as the conjoined and hypertrophied adventitial coats of the pial vessels, the lymphatic spaces of which have undergone a special development so as to form a spongy lymph sac."[4] More recently W. F. Robertson has altered his opinion as to the naked condition of the arterioles. He now holds that they are possessed of a delicate adventitial coat, and maintains that this additional observation is in no way out of harmony with the general spirit of the above doctrine.[5]

In many cases it is impossible to make out any

adventitial layer; and immediately under the muscular coat appear round, oval, or spindle-shaped spaces of small size and lined by an endothelium. In other cases, again, a very thin layer of longitudinally disposed fibres of connective tissue may be seen, and I feel assured that an adventitial coat exists, though in places so thin as to be discerned only with difficulty or not at all. The presence, moreover, of such is further proved when, thickened by hyaline degeneration, the adventitia appears as a well-marked regular band beyond the muscular coat, even in arterioles with only one layer of muscular cells. Beyond the adventitia, now and then, appearances, as of a continuous layer of endothelial cells, may be made out, or a longitudinal channel lined by such cells seems to exist between two small arterioles. Such a condition, however, does not appear to me to imply the existence of a special lymph sheath, but is most probably produced by one of the spaces of the "spongy lymph sac," altered in shape to suit the exigencies of the case. Albarran[6] considers the vessels of the choroid plexus as destitute of a lymphatic sheath. Moreover, one can see no necessity for such if the contention of Middlemass and Robertson be correct—that "the whole pia-arachnoid may be looked upon as the conjoined and hypertrophied adventitial coats of the pial vessels, the lymphatic spaces of which have undergone a special development so as to form a spongy lymph sac."

The intima of the small arterioles is likewise very thin, the endothelium being separated from the muscular coat by a very delicate layer of tissue. W. F. Robertson[5] holds that the elastic coat has normally no existence in the small cerebral arterioles. I cannot, however, agree with this, and it seems to me that even the smallest arterioles possess a fine elastic lamina. Indeed, in the normal condition the intima consists of practically nothing else but endothelium and elastic lamina.

Capillaries—The capillary network is best marked at the surface of the plexus, immediately under the epithelium and in the villi, but may be traced throughout a great part of the plexus. The more central parts of the glomus,

however, show no such network, and the tissues here are practically non-vascular. The capillaries are of large size and are likewise surrounded by the spaces of the pia-arachnoid, and in parts little more than two layers of endothelial cells—that of the capillary itself and that of the space—seem to separate the cavity of the lymph sinus from the interior of the capillary. There is no reason to believe that the minute "vasa serosa," described and figured by Luschka[7] in this structure, have any real existence.

The capillaries here, moreover, are remarkable for the fact that they possess a special adventitia in addition to their endothelial intima. There are two forms of nuclei in these capillaries, elongated, and rounded. The former belong to the intima, stain faintly and do not project from the capillary wall; the latter, on the other hand, are adventitial, stain deeply and do project. This adventitial investment must be considered as consisting of two elements, connective tissue cells and exceedingly delicate fibrils, the latter being continuous with the connective tissue of the adventitia of the larger vessels. These fibrils in the capillary walls are of great importance, for it is in them, as Woodhead[8] points out, that the process of waxy degeneration is supposed to occur. Small capillaries, too, may be normally seen immediately under the muscular coat of arteries and arterioles and quite close to the intima of veins.

Veins.—The veins are very numerous, and so frequent are their windings and bendings that there almost seems to be in the glomus an arrangement of blood sinuses approaching the character of cavernous tissue. In sections the blood spaces appear large and very irregular in shape, and though at first inclined to attribute these to the presence of a cavernous arrangement here, I am now convinced that numerous and very tortuous veins are all we have. The veins are lined by an endothelium and have remarkably thin walls, which are devoid of muscular tissue. The fibrous tissue of the walls very quickly merges into the surrounding spongy tissue, and spaces lined by

an endothelium are seen quite close to the intima. Indeed, the wall of a vein might be said to be composed of only a more compact pia-arachnoid tissue.

Villi.

The surface of the choroid plexus is beset with a large number of highly vascular villous projections. These are of all sizes, and the largest may branch and subdivide many times before the ultimate villi are formed. Where the plexus does not present such a shaggy appearance to the naked eye, small non-branching villi may be seen closely arranged alongside one another.

Each larger villus has an afferent artery and efferent vein. These open into a capillary network lying near the surface, and in the ultimate villi a capillary loop, in the form of a bow, may be seen close under the epithelium, which everywhere covers the plexus. The same capillary may pass through more than one villus. The greater part of the villus structure consists of epithelium and capillary, the smaller remainder being made up of homogeneous connective tissue, with a few oval, spindle, or ramifying corpuscles. Occasionally, however, this tissue appears fibrillated, but only in the very largest villi can spaces and trabeculæ be made out, a loose areolar tissue being more commonly observed.

Epithelium of the Choroid Plexus.

The free surface of the villi and of the depressions between them is everywhere covered by an epithelium.

Hæckel[9] regards the epithelium as composed of a single layer of cells, but in pathological conditions he has seen these cells greatly increased in number. Heldt[10] likewise describes only a single layer of pavemented epithelium, and denies the existence of several layers. With Hæckel and Heldt may be classed Schäfer, Dejerine,[11] Koelliker,[12] and others.

Luschka,[7] on the contrary, has described this epithelium as approaching the stratified formation, recognising not only two or three layers of cells situated above one another, but also different developmental forms.

In many places it can be demonstrated that only a single layer is present, but then just as often three, four, or more layers may be seen, the two conditions lying alongside one another. Hæckel, we saw, regards the latter state as due to pathological proliferation of the epithelium. Such, however, I cannot believe. The existence of several layers of cells seems too common to be accounted for in this way, being found in all my cases in parts without exception, and also in the choroid plexuses of sheep, calves, and oxen examined. Beyond a doubt several layers of cells normally exist, and may be traced through their different stages of transition as we pass to the surface. Moreover, in a few human plexuses I have seen the deeper and more active cells in actual process of division, still further demonstrating, as Luschka held, that there are not only two or three layers of cells situated above one another, but also different developmental forms. Where only one layer of cells exists I must suppose that the others have been brushed off, though I have to admit that narrow spaces covered by, and apparently unable to contain more than, a single layer of epithelial cells are found. It is possible, however, that the contraction of the tissues, in process of hardening, has altered the character which such a space possessed during life. These epithelial cells form a transitional rather than a stratified variety of epithelium, for the outermost cells never show any tendency to become flattened.

The individual cells vary in size, ranging from a little less than ·01 to ·015 mm. They are irregularly rounded or polygonal in shape, and when an epithelial surface is seen on the flat, they present an appearance like a piece of mosaic work. They fit closely by means of delicate processes which interlock between neighbouring cells. Henle has described these processes—which he terms "prickly"—as locking into suitable cavities in adjacent cells like a wedge. In the deepest layer small and slender processes may be seen coming off from the base of a cell at the angles and penetrating into the sub-epithelial layer. This last fact was first pointed out by Henle, and is of considerable importance

as tending to support the view that the epithelium of the choroid plexus is homologous with the ependymal epithelium, which has such processes even in adult life. There are no cilia on either the cells lining the plexuses or the ependyma of the ventricles, but such are generally believed to exist in embryonic life. The protoplasm of the epithelial cell is very granular and contains a large round nucleus, likewise granular, in which a nucleolus can occasionally be distinguished. In addition there is usually present a clear-yellowish, or even brownish-coloured, highly refractive globule, sometimes approaching the dimension of the nucleus itself, but as a rule only attaining to a third or less of that size. By means of an oil immersion lens it may be seen that the granular appearance of the protoplasm is in reality due to an immense number of small globules, which appear to be of the same nature as the large one. Where there are several layers of cells *in situ* it may be made out that this vacuolation increases steadily as we pass to the free surface, until cells are reached entirely transformed into globules and showing no nuclear staining. Beyond this, again, the cells discharge their contents by breaking up, sometimes leaving an empty cell membrane to indicate where they have been. Before the cell actually breaks up the globules may run together to form a single large sphere. In celloidin preparations, where the ventricular fluid has got entangled in the recesses of the plexus, numerous droplets, clear and pigmented, and in every way similar to those met with in the epithelial cells, may be seen lying free on the surface; while here and there these same droplets appear to be running together to form larger drops.

The single globule, so often seen in the protoplasm with ordinary powers, almost invaribly becomes darkened on being treated with osmic acid, while the granules also are blackened. This reaction has led Obersteiner[13] and others to regard them as being of a fatty nature, and it seems to me some relation to a fatty substance may be inferred. Haeckel[9] accounts for the presence of the pigment in the epithelial cells by accepting the same view and then supposing a "transformation from fat into pigment, as has

been already demonstrated in the case of certain other pigment granules." But there is, to my mind, no reason why we should not accept the pigment colouring the globules—or even the pigmented granules occasionally found—as normal to the epithelial cells, especially in conjunction with the frequency of normal pigmentation in the elemental tissues of the brain and its coverings.

Nerves of the Choroid Plexus.

Purkinje[14] has described a retiform arrangement of fine nerve fibres in the pia mater. Koelliker[12] has found that these nerves always follow the course of the arteries, and though he has never recognised them in their endings, he has traced them into the substance of the brain along with small arterioles. He states, however, that no nerves are to be found in the vessel plexuses of the brain, though he mentions that Bochdalek has seen fine nerve twigs in the choroid plexus of the fourth ventricle, these twigs proceeding from the roots of many cranial nerves.

In 1873 Benedikt[15] likewise described nerves in the plexus of the fourth ventricle. "From the medulla oblongata and also from the large multipolar cells in the restiform body, a small strap-shaped nerve bundle goes out into the choroid plexus of the fourth ventricle. This bundle consists of doubly contoured fibres, which pass out into the vessels of the plexus for vaso-motor purposes. In gold preparations these nerves may be seen in the neighbourhood of the larger vessels, and in the region of the smaller ones they appear as a terminal network of nerve fibres. Fibres also went out to the epithelial cells, but nothing can be said about the endings of the nerves." In 1874 Benedikt[16] traced these fibres to the vagus nucleus.

Since a nerve plexus has been demonstrated in the pia mater and in the choroid plexus of the fourth ventricle, one would expect by analogy to find a similar condition in the choroid plexuses of the lateral ventricles, but such has not to my knowledge been described.

It may be seen, however, that medullated nerve fibres do exist in the plexuses of the lateral ventricles, though

they are present in very small numbers. I have not been able to trace them for any distance, and can say nothing as to their relations and distribution but that they seem to lie in the deeper parts of the plexus and sometimes in the neighbourhood of vessels. Both in man and the calf these fibres were brought into view by W. F. Robertson's modification of Heller's method. It seems not at all improbable that, as in the plexus of the fourth ventricle, these are vaso-motor nerves destined for the blood vessels.

Pathology of the Choroid Plexus.

The choroid plexus is liable to be affected by many pathological changes. Each individual tissue may be attacked, or the lesion may be more or less common to the entire plexus. "The tumours are chiefly of the mesoblastic or connective tissue type, but epithelial or carcinomatous growths are also met with." Among the former Ziegler describes the following: "Sarcoma, alveolar sarcoma, endothelioma, myxosarcoma, myxoma, angiosarcoma, angiomyxoma, angiomyxosarcoma, angioma and psammoma, while more rarely fibroma, lipoma, chondroma, and cystic fibroma are present." Secondary growths of every kind are found, and of animal parasites may be mentioned the echinococcus and cysticercus.[17] Cholesteomata are rarely seen in the human subject, but seem to be somewhat common in the horse, where they may attain an enormous size.[18]

I have not had an opportunity of examining any of the above-mentioned conditions, and will now proceed to describe those changes which I have met with in the course of my investigation.

(*a*) *Concentric Bodies.*

These structures are very common in the choroid plexus. I have found them in every human case examined. They are often present in enormous numbers, and Heldt[10] has regarded them as being in great part normal and physiological. They have been described under different names: brain sand, acervulus cerebri, concentric concretions, hyaline

concentric bodies, &c., and much difference of opinion has existed as to their mode of origin and composition.

In none of the choroid plexuses from the sheep or ox was I fortunate to meet with any of these bodies, though in the calf I, on one occasion, found what I took to be early developmental forms. Luschka has observed them in rabbits, dogs, and horses.

Similar concentric bodies are found in all the membranes of the brain and spinal cord, and constitute the chief element in those tumours called psammomata.

The usual form of these bodies is round, and, as a rule, they are surrounded by a well-marked hyaline capsule, or even a capsule of fibrous tissue with long, thin, spindle-shaped cells. They are marked with numerous concentric rings, these markings varying in intensity and number in individual bodies. Though the most common, this is not the invariable shape, and many different forms may be produced from several spheres coming together. Thus we may have a dumb-bell or trefoil-shaped structure, the interior showing distinct concentric bodies with rings of their own, while beyond these the body is surrounded by a common stratification. Rod-shaped bodies are occasionally seen, but they are decidedly rare. Irregularly ramifying forms, as described by Luschka, Hæckel and Koelliker, I have never seen.

Heldt, as the result of his observations, states that all these bodies show a thoroughly round shape. He is, I think, in the main right. All of them—with the exception of the rare rod-like forms—show a thoroughly round shape, or a combination of several such shapes, resulting in a more or less irregular figure, but one, however, which can always be resolved into a collection of spheres. They likewise vary very much in size, and are found in the plexuses ranging from ·01 to ·15 mm. in diameter.

Apart from their concentric markings, these bodies are, as a rule, structureless, but now and then the forms of globes or spheres can be made out in their interiors, though in many cases nothing more than a few granules are seen. Hæckel, however, found as the nucleus of such bodies

nucleated cells, fat and pigment granules, heaps of shrivelled blood corpuscles, and rarely corpora amylaceæ. It is often possible to make out cells swollen from hyaline degeneration in the centre of these concentric bodies, but their nuclei are never visible. I have, however, never seen any appearances suggesting that blood corpuscles or corpora amylaceæ might form the nuclei or beginnings in the development of the same (concentric bodies).

In eosine and hæmatoxylin preparations they usually take on a bright-red colour, though sometimes the centre is coloured blue, while the periphery alone shows the eosine staining. In the same body, moreover, the different concentric rings may take up the eosine with different degrees of avidity. Carmine stains these bodies deeply, though in picro-carmine preparations here and there yellow rings are observed inside the red body, while the very small bodies are alone stained by the picric acid. Van Gieson's stain colours them a bright red, due to the fuchsine present in it. In the same way the fuchsine in the Ehrlich-Biondi stain attacks the concentric bodies, making them stand out in a remarkable manner from the surrounding faint-red or green-coloured tissue. The hyaline droplets, which are found in abundance around the concentric bodies, and which represent a phase in the development of the latter, do not take on the red fuchsine staining, but stain a dirty-green colour with the methyl green. Weigert's fibrine stain occasionally colours these concentric bodies, along with the hyaline connective tissue trabeculæ, a deep-blue colour, while the surrounding tissue remains unstained. These formations have never shown in any of my cases a waxy reaction with methyl violet. Osmic acid distinctly darkens these structures, sometimes bringing out a granularity not before evident, or accentuating the concentric markings.

All the older writers, including Obersteiner, Haeckel, Luschka, and Heldt, describe these bodies as concretions composed of carbonate of lime and carbonate and phosphate of magnesium. Heldt, however, lays special emphasis on the fact that there are also hyaline concentric bodies, which have not yet become calcified, present in the choroid plexus.

Aqueous solutions of mineral acids and acetic acid have practically no action on these structures; but if strong hydrochloric acid be used, a brisk effervescence takes place in many cases. Other concentric bodies, however, give off no gas on being treated with hydrochloric acid.

After examining my sections, I am of opinion that these bodies are not merely deposited from the tissue fluids, as Virchow[20] and others think, but that here we have an active proliferative process followed by a degenerative one. It has been already mentioned that the pia-arachnoid is a spongy lymph sac, made up of trabeculæ lined with endothelial cells. To begin with, probably as the result of some chronic irritative process, a proliferation of the endothelial cells occurs, and these cells may be seen undergoing division by the process of karyokinesis. In eosine and hæmatoxylin preparations the following phases of degeneration may be traced subsequent to the proliferation. The cell plate first of all swells up and becomes homogeneous, staining a very faint blue, while the nucleus has an increased affinity for hæmatoxylin. Next the protoplasm of the cell becomes possessed of an increased attraction for eosine, and usually has a somewhat granular appearance. Then the eosine staining becomes fainter and less granular, and with an oil immersion lens it can be made out that the protoplasm has formed inside the cell very numerous hyaline globules which, at first separate, eventually run together. The nucleus now loses its affinity for hæmatoxylin, stains more faintly, and in part shows the eosine colouration. This progresses gradually, till finally the nucleus is altogether coloured with eosine, being darker than the hyaline cell-plate. Afterwards this distinction is lost, and nothing is seen but a homogeneous hyaline sphere staining faintly with eosine, and measuring in diameter ·01 to ·05 mm. One of these spheres may form a concentric body, and numbers of such with only one concentric mark—doubly contoured spheres—may be seen. As a rule, however, these spheres, probably of a semi-fluid consistence, coalesce to form the more usual concentric body In many cases the cells take up this position before degenerating,

and in a space a regular whorl of cells is seen, in appearance like a "cell nest," or as Ziegler puts it, like the skins of an onion. All stages of degeneration may be met with in these, from the swollen cell with the dark-blue nucleus to the homogeneous hyaline sphere. Nor does it seem necessary that these hyaline spheres should form concentric bodies in the identical spaces in which they are developed. It appears not at all unlikely that they may be carried along in the lymph stream circulating through these spaces till arrested by some obstruction. Indeed, the position and arrangement of many suggest this. Behind such an obstruction other hyaline spheres will be constantly added, and the never-failing pressure applied from behind will be sufficient to weld them into a single large mass, while probably, as W. F. Robertson indicates, the concentric rings appear subsequently owing to shrinkage.

The fibrous capsule so frequently present is added later, after the manner in which nature encapsules all foreign bodies; and in all probability the fibrous tissue owes its origin to the still healthy endothelial cells. There is never any round-cell infiltration around these bodies, the cellular aggregations in their neighbourhood being endothelial in character. Nor is there any need of such a round-cell infiltration to explain the subsequent development of the connective or fibrous tissue capsule, as "the endothelial cells," according to Metchnikoff,[21] "are actively engaged in the formation of new connective tissue."

This proliferation and degeneration of the endothelial cells may occur anywhere throughout the plexus, but is most marked in the glomus, where, too, the normal trabecular arrangement of the pia-arachnoid can be most perfectly made out. In the same way cells may proliferate and degenerate, and concentric bodies may form in the spaces close to the vessel wall; but, so far as I can see, there is no special tendency to the occurrence of them here. When concentric bodies develop in spaces immediately outside a vessel, they may by pressure seriously obstruct it, or lead to the absorption of a hyaline adventitia. These facts probably account for the description of buddings or ampullary dilatations of

the walls of the blood-vessels of the choroid plexus by Cornil and Ranvier,[19] and also for the further idea that the incrustation of these buds by lime salts formed the concentric bodies. Heldt came nearer the truth when, denying the presence of buds on the vessels, he attributed the formation of these bodies to a hyperplasia of the adventitia, consisting of connective tissue-cells and stratified molecular mass, and forming excrescences on the vessel wall. At no time, however, do these bodies develop in the adventitia, but always in the lymph spaces beyond.

While the above is the most common mode of development of concentric bodies, I do not think that it is the invariable one. When hyaline degeneration attacks the arteries and capillaries, these sometimes become converted into solid tubes. This condition, though in all likelihood happening often, is but rarely met with, suggesting the idea that some further change occurs in these solid hyaline vessels. These hyaline cylinders most likely split across, while the segments contract into the form of rounded masses, which later acquire concentric markings.

Very frequently, too, in the midst of concentric bodies, hyaline rings are met with containing degenerating cells in their interiors. It is impossible to resist the conclusion that these hyaline rings are developmental forms of concentric bodies. The hyaline circle is of varying size and thickness, and may show concentric markings with spindle-shaped cells between the different layers. The interior of such a ring may be lined or packed with cells, all more or less showing signs of breaking up, with diminution or loss of nuclear staining. It is difficult to trace the origin of such a condition, and the different appearances are most conflicting and confusing. In a few cases it has been possible to demonstrate that these are merely depressions from the surface epithelium—what may be termed acini in transverse section—somewhat similar figures in longitudinal section allowing the continuity of the epithelium to be traced. But this explanation does not satisfy for all. Thus, a small hyaline ring with a single degenerating cell in its interior could not represent a prolongation from the surface, and most probably

is a hyaline capillary in transverse section with a contained endothelial cell. Others which are larger most likely represent small hyaline arterioles or venules, with degenerating endothelial cells in their interiors; and in a few cases this can be conclusively proved by the detection of blood corpuscles in the lumen of such a structure.

In conclusion, it may be stated that the majority of these concentric bodies are composed of hyaline material, this being more especially brought out by their reactions with eosine and fuchsine. But this hyaline material seems to be an exceedingly unstable substance, leading at times to considerable variations in staining. Thus is the fact explained that in eosine and hæmatoxylin preparations these bodies on occasions show a preference for the latter, and take up the former with different degrees of avidity. In the same way the reactions with Ehrlich-Biondi, and the occasional colouring with Weigert's fibrine stain, are accounted for. The conclusion, therefore, of Alzheimer[22] seems borne out "that the colloid substance"—in this case synonymous with hyaline—"in the tissues undergoes transpositions, and becomes altered in its reaction and chemical property." But these bodies are not all hyaline, as the effervescence with hydrochloric acid proves. Some of them are concretions, but they are decidedly in the minority, and are only met with in abundance in senile cases. In cutting tissues not previously decalcified, the simply hyaline bodies cut easily, and offer no resistance to the knife, while the concretions will not cut, and tear or break up the tissue. There is not much, however, in the microscopic appearances, apart from a more or less marked granularity in the latter, to distinguish between them. Both are alike, and the only reliable test is the chemical one with hydrochloric acid. Moreover, it seems not at all unlikely, from the reaction with osmic acid, that these hyaline concentric bodies preparatory to their calcification undergo a retrogressive fatty change, as so frequently happens in the case of calcifications elsewhere.

In my experience—which is also the experience of W. F. Robertson[23]—these bodies are never found in such profusion in the mentally sound as in the insane.

(*b*) *Mulberry Bodies.*

Closely allied to concentric bodies are structures which were first described by W. F. Robertson[23] in the dura mater under the name of "mulberry bodies." These bodies are also found in the choroid plexus. In comparison with the hyaline concentric bodies they are rare, but when present may occur in enormous numbers. They consist of groups of rounded or oval cells, which stain of a deep purple colour in hæmatoxylin and eosine preparations, and are perfectly homogeneous in appearance. The individual cells are pretty uniform in size, possessing a diameter of about ·01 mm. Each group may or may not be surrounded by a capsule. This capsule in some cases is only perceived with difficulty and, as a rule, is very faintly stained. Occasionally, however, it presents a deeper staining, and when this occurs the cells in the interior are more massed together, and discrimination between them is difficult. Mixed up with these mulberry bodies are isolated cells of the above description, which may or may not have a capsule, while all around are fully developed hyaline concentric bodies and pale hyaline spheres.

W. F. Robertson expresses no opinion as to the origin of these bodies, but I think I have traced the process by which they are produced.

Each little oval purple-coloured body represents a degenerated endothelial cell, and may be seen in process of formation in the spaces of the choroid plexus. It is likewise a hyaline degeneration of the endothelial cells, and this anomalous staining, as already seen, is no unusual feature of hyaline material. These little bodies, then, run together and form a mulberry-like mass, which later acquires a capsule. In all probability this capsule or envelope is elaborated not by these cells themselves, but is deposited around them from the fluid in which they are bathed. In their neighbourhood are seen large hyaline spheres, staining faintly, irregular in shape, and breaking down or gradually merging into the fluid about them. This capsule, at first indistinct, becomes more and more

marked, till finally it assumes a very decided hyaline appearance around the mulberry mass. The oval bodies now begin to merge into one another and become less distinct. Then concentric rings appear in the middle of such a structure, and forms are seen with concentric markings in their interiors, and still surrounded by the oval purple-coloured cells. These likewise lose their identity and assist in the formation of a hyaline concentric body, which is the consummation aimed at.

I have gone somewhat fully into the development of these mulberry bodies and their further conversion into hyaline concentric bodies, because W. F. Robertson writes of them as though they were distinct entities. But such I have shown them not to be. They only represent another mode of expression of this hyaline change, which may occur under many different forms, and produce a material having very various staining reactions.

(c) *Cystic Degeneration of the Choroid Plexus.*

This is a very common condition, being found in a large proportion of cases. Indeed, so frequently are cysts present, that Faivre,[24] writing in 1855, described "choroid vesicles" as normal and peculiar to the human subject. It is interesting, on the other hand, to note that, as early as 1826, Robert Hooper, M.D., figured these cysts of the choroid plexus in his "Morbid Anatomy of the Human Brain (being illustrations of the most frequent and important organic diseases to which that viscus is liable)." Of my sixty-five cases examined, cysts were present in thirty-seven, while Ogston[25] only found them in 19 per cent. of the brains of known drunkards.

The glomus is pre-eminently the seat of this cystic degeneration, and cysts, though occurring, are never found to any extent in the other parts of the plexus. These cysts may be little larger than a pin's head, or may reach the size of a pea. In some cases they are few in number, in others they are very numerous, the whole glomus being converted into a cluster of cysts like a bunch of grapes

in miniature. I have never seen them so large as a hazel nut, as Luschka describes, though the glomus itself may attain such dimensions. Cases are on record where cysts of the choroid plexus have reached an enormous size, distending the ventricles, pressing on the surrounding brain, and eventually causing death.[26] [27]

The walls of the cysts are thinner in some places and thicker in others, but everywhere delicate. They are very vascular, and numerous fine vessels may be seen coursing over the surface of the little bladders. The walls are further remarkable for the presence of a fine white dotting, due to concentric bodies embedded in them, or to small aggregations of cells filled with fatty granules. In one case a white patch, about half the size of a split pea, was seen at the apex of a cyst. On microscopic examination this was found to be composed of large cells filled with fatty granules, which were darkened on the addition of osmic acid.

The cysts have a smooth shining surface, and, as a rule, present no villi. As a result of the distortion caused by this swelling, vessel loops, attached by small mesenteries, are to be seen projecting from the surface of the glomus in greater numbers than they normally do.

The tissue of the walls is composed of a connective tissue stroma in which run numerous vessels, arterioles, venules and capillaries. This connective tissue forms in parts quite thick bands, which are produced by the obliteration of the normal spaces between the trabeculæ. The surface of the cyst, moreover, is very often destitute of an epithelial covering. Near the base of such a cyst the epithelium may be quite distinct, but as the apex is approached the cells become scattered, a bare patch showing up here and there, till finally a portion is reached where no epithelial cells can be seen. It is an open question as to how far such a condition is brought about artificially, and there can be no doubt that, in the handling of the tissues after death, the epithelium on the most exposed parts will be very liable to be rubbed off; still, from the frequency with which it occurs, I am inclined to the opinion that it is not altogether an "artefact."

The interior of the cyst is made up of a very open network of connective tissue trabeculæ, which are lined by degenerated and degenerating endothelial cells, scarcely one of which presents normal features. The spaces are filled with a thin fluid, in which float cells in different degrees of degeneration. Concentric bodies are of very frequent occurrence throughout the cyst, and may be found packed in the meshes over quite a considerable area. All around this looser and more open network, and gradually blending with it, is a dense tissue in which there has been very extensive proliferation of the endothelial cells lining the trabeculæ, and associated with this usually some thickening of the trabeculæ themselves. The proliferated cells, moreover, even in the quite dense portions, usually show early degenerative changes.

In the fluid which fills the cyst the following formed elements are suspended: (1) endothelial cells with an increase in the granularity of their protoplasm, the granules stained deeply with eosine, may or may not obscure the large oval nucleus; (2) cells showing one or more vacuoles in the protoplasm, with an occasional cell in which the nucleus is also vacuolated; (3) large globular cells whose contents consist almost entirely of a hyaline, perfectly homogeneous, and more or less opaque sphere, surrounded by a small circular or sickle-shaped zone of granular protoplasm, which contains a nucleus; (4) large homogeneous globules, in which the appearance of a cell wall may still be traced, but containing no other formed element; (5) still larger homogeneous hyaline spheres with no indication of cell membrane; (6) doubly contoured hyaline spheres, the inner sphere probably representing the transformed nucleus, the outer being derived from the cell protoplasm; (7) free nuclei, or nuclei with remnants of cell membrane and even protoplasm attached; (8) irregular masses of hyaline material; (9) extravasated and disintegrating blood corpuscles and granular *débris* derived therefrom; (10) hyaline concentric bodies of all sizes.

The above elements, with the exception of No. 9, arise from the endothelial cells lining the trabeculæ as the result

of a degenerative process, and the following sequence of events may be traced. The endothelial cell first of all swells up, and the cell plate becomes coarsely granular, presenting in hæmatoxylin and eosine preparations numerous eosinophile granules. A vacuole now appears, encroaching more and more upon the protoplasm, till the granular contents of the latter are represented only by a circular or sickle-shaped mass at the edge of the cell. A nucleus may or may not be seen, and may appear to float in the vacuole, or remain attached to the cell wall embedded in the granular protoplasm. Then, very commonly the cell membrane ruptures and the contents are discharged into the lymph spaces, while in the fluid the free nuclei may be seen. The cell may, however, not rupture at this stage. The nucleus itself may become vacuolated and assist in the general distension of the cell, till nothing is seen but a homogeneous globule with a faint remnant of cell wall and protoplasm. In other cases the whole cell presents a coarsely granular appearance. These homogeneous globules thus produced may swell up still further till they rival the concentric bodies in size, and could the individual stages not be traced, one would be inclined to think with Alzheimer[22] that these large hyaline spheres are really elaborated from the tissue fluids, and not, as I believe, actually produced by cell degenerations. These large hyaline spheres may rupture, perhaps adding to the fluid contents of the cyst. More certainly, however, they run together, forming large irregular masses of hyaline material.

The connective tissue trabeculæ may become hypertrophied, and very frequently they undergo hyaline degeneration. And often owing to the pressure of the degenerated cells and fluid, these trabeculæ become broken down and absorbed, leading to the formation of spaces of large size, while, here and there, lying in the midst of hyaline spheres, may be seen free portions of the connective tissue trabeculæ.

The above are the microscopic appearances to be met with in the cysts of the choroid plexus, and as the result of my own observations I have arrived at the following conclusions as to their origin.

Hyaline concentric bodies are very commonly found in cysts, likewise the hyaline spheres, which have been shown to take part in the formation of concentric bodies. The degenerative process in the endothelial cells of the trabeculæ in cystic formation is very similar to that which precedes the development of concentric bodies. Indeed, so close is the resemblance that it is very questionable if we are entitled to discriminate between them. Still, to my mind, it is quite clear that cells break down into fluid in the cysts in a way that never occurs apart from them. But such degeneration of cells alone does not seem sufficient to account for the development of these cysts, though there is no doubt that the fluid found in them is in part due to this bursting of the endothelial cells affected with colloid or hyaline degeneration. In all the cysts I had an opportunity of examining the fluid was quite limpid. Colloid cysts, with gummy, viscid contents, have, however, been described by Wallmann[28] and Hoffmann.[29]

It seems more than probable that there are two processes here at work, a primary proliferation and degeneration of the endothelial cells, associated frequently with hyaline changes in the trabeculæ, and a secondary condition of œdema added thereto. Still, I do not think that Haeckel is accurate in saying that this solid structure—produced by proliferated cells and thickened trabeculæ—"may become through serous infiltration softer and more watery, and eventually form a bladder," for in my opinion the cyst is formed not in but behind this thickened mass. Moreover, he is wrong in attributing the cell formations to the connective tissue corpuscles.

Through the spaces constituting the pia-arachnoid, of which the choroid plexus is composed, there must be a constant circulation of lymph. This proliferation and degeneration of cells in many cases completely fills up these spaces, and a serious obstacle to the flow of lymph must result. As shown, too, when dealing with the formation of concentric bodies, hyaline spheres may travel till they stick in these spaces or channels, eventually blocking them up. Concentric bodies must have the same effect, and these are

never present in any numbers without a concomitant development of cysts. There exist, then, very numerous points of obstruction behind which the lymph stream is constantly pressing. There is, in short, an obstructive œdema. The spaces of the pia-arachnoid become more and more distended with the lymphatic fluid, and larger spaces still are produced by the breaking down or absorption of intervening trabeculæ, while the cyst itself is produced by a number of such spaces lying adjacent to one another. The degenerated cells add to the fluid their quota, and where the tendency is for the cells to rupture in the manner described, then are the contents of the cyst colloid. In other cases, again, where the greater number of the degenerated cells goes to the formation of concentric bodies, the cystic fluid tends to be thin and limpid. Finally, such a collection of fluid may be shut off from surrounding parts by the occurrence behind the fluid accumulation of the same changes which led to the obstruction in front, and the frequency with which dense tissue is found all around the cyst seems to point to such a conclusion.

This is practically in harmony with Ziegler's idea that "the cysts of the pia mater would appear to depend on the presence of closed lymph spaces, congenital or acquired, in the pia mater or subarachnoid tissue," and in the case of the choroid plexus we see very distinctly how such closed lymph spaces may be produced.

So far as I can see, there is nothing in the position of these cysts to bear out the view of Luschka and Schnopfhagen,[30] that "they are due to the dropsical separation from one another of the two layers of the pia mater which constitute the tela and choroid plexus." Now and then a separation seems to occur, but can always be explained by the breaking down of trabeculæ and the joining together of numerous spaces to form a single large cavity.

No more can I agree with the opinion of Schrant and Förster,[31] that "the epithelial cells become converted into large and delicate albuminous cells, which then form colloid cysts." There is a constant change going on in the epithelial cells, and they normally undergo a process of vacuolation

and rupture to form the choroid plexus secretion. With such factors at work one would expect *a priori* to find frequent examples of retention cysts. Appearances suggesting such are frequently seen both in man and the lower animals. But they never attain any size, and instead of actual retention cysts we may be seeing only the lower parts of the tubular depressions found between the villi, in the depths of which tubes secretion, though not actually held back, would be apt to lodge.

(*d*) *Thickening of the Trabeculæ, with Proliferation and Degeneration of the Endothelial Cells.*

I have described, first of all, the degenerations of the choroid plexuses leading to the formation of hyaline concentric bodies and cysts, as these are the most remarkable, but the endothelial cells and trabeculæ proliferate and degenerate to other ends.

"A milky and opaque condition of the pia-arachnoid is very common in the insane. In the majority of cases it is a well-developed state, and its absence is quite exceptional." (Robertson.)

Similar conditions are found in the choroid plexus, and are likewise very common. These changes are always more marked in the glomus, where the trabecular arrangement is on a larger scale and unequivocal.

Hyperplasia and Hyaline Degeneration of the Fibrous Tissue Trabeculæ.—The fibrous tissue trabeculæ undergo a slow hyperplasia, and are found in all conditions. In some cases the thickening is slight, the fibres being little more than swollen. In others, again, there is a distinct connective tissue overgrowth, and localised areas of dense fibrous tissue are produced, in which the normal pia-arachnoid spaces are obliterated or merely represented by endothelial cells. These altered and new formed fibres are very prone to undergo hyaline degeneration, and much thickened strands staining very brightly with eosine, and even large hyaline masses, may thus result.

Osteoid Plates.—On three occasions I found small osteoid

plaques, distinctly laminated, and penetrated by well marked Haversian canals carrying blood vessels and numerous cells. In none of them was there any deposition of calcareous salts.

Hyaline Degeneration of the Connective Tissue in the Smaller Villi.—Before leaving the connective tissue alterations it will be convenient to describe hyaline degeneration of this structure in the smaller villi. Here, as already mentioned, the connective tissue is represented by a homogeneous matrix with very few cells: no trabeculæ or spaces can be made out. Now and then the tissue is fibrillated, while very occasionally distinct connective tissue fibres are seen.

Hyaline degeneration frequently occurs in this homogeneous connective tissue. The substance between the epithelium and the capillary loop swells up, acquires a more dense appearance, and stains very deeply with eosine. This increase of tissue finds room for itself by encroaching on the lumen of the capillary, which may eventually become obliterated altogether, leaving no trace behind it. Very often associated with this condition is a similar change in the capillary itself; and obstruction of the little vessel may really be brought about by a process of thrombosis. But soon this appearance of thrombus is lost, the clot becomes converted into hyaline material, and may even take part in the formation of a concentric body. When the villus becomes throughout hyaline and is robbed of its blood supply, the epithelium is almost invariably found shed. This desquamation, moreover, may occur while the capillary loop is still present, the intervening hyaline mass cutting off the source of nourishment from the epithelium. Villi over large tracts are found bared of their epithelium, and though at first enlarged, they eventually become much shrunken and distorted. This is a very common condition in senile insanity, and I would make the suggestion that, when spread over a large area, it may account for the atrophy of this organ so frequently seen in these cases.

Proliferation of the Endothelial Cells.—Associated with this change in the fibres there is proliferation—and degen-

eration—of the endothelial cells. When the thickening of the connective tissue trabeculæ is extreme, the changes in the endothelial cells are slight, or may be entirely absent. The endothelium is very commonly found shed in cases where the connective tissue fibres are thickened and the arrangement of spaces maintained. The proliferated cells frequently form dense masses in the spaces of the choroid plexus. This is not a round-cell infiltration, but is caused directly by a multiplication of the endothelial cells lining the trabeculæ. These endothelial cells may rarely be seen in actual process of division, and though often the nuclei in these cellular collections are rounder and smaller than those of the ordinary endothelial cells, it can be made out that in the main they resemble the endothelial type.

In connection with this condition occurring in the arachnoid in certain mental disorders Ziegler states that it is still doubtful whether these "milky thickenings" are always of inflammatory origin. "They are histologically due to fibrous thickening, endothelial hyperplasia, or more rarely to cellular infiltration." In the pia mater itself, he holds that these changes, in their later stages at least, are unmistakably inflammatory and accompanied by accumulations of leucocytes, especially around the vessels.

W. F. Robertson,[4] on the other hand, is very definite as to these aggregations being composed of endothelial cells entirely, and is of opinion that areas of small round-cell infiltration upon the vessel walls or elsewhere seldom occur. "It is only," he adds, "in advanced general paralysis, in syphilitic insanity, and in the very rare and still obscure condition known as purulent infiltration of the pia-arachnoid, that such an aggregation of round cells is added to the other appearances."

I cannot but favour the view of these collections of cells being endothelial in character, and though two syphilitic and seven general paralytic cases were examined, only in one of the latter was I able to detect round cells upon the vessel walls and in the midst of the endothelial proliferations.

Degenerative Changes in Endothelial Cells.—These pro-

liferated endothelial cells by and by undergo degenerative changes, and these same changes may be observed without any previous cell multiplication.

(*a*) A very common degenerative process consists in the endothelial cells simply breaking down into granular *débris*, and spaces are frequently seen crammed with such material.

(*b*) Fatty changes are likewise often observed, and may be present over considerable areas. This condition is shown by the presence in the cell plate of numerous bright and highly refractive little globules or granules, which are darkened by osmic acid. Sometimes a nucleus can be distinguished amidst these fatty granules, in other cases it is impossible to do so. Cells thus affected may attain very considerable dimensions, a diameter of ·025 mm. not being at all uncommon.

Haeckel describes this as not a rare condition, "especially in association with the proliferating cystoid metamorphosis and hypertrophy of the connective tissue."

I am of the like mind, but feel convinced that he is wrong in saying that this fatty change occurs in the connective tissue corpuscles.

W. F. Robertson[4] and Adler have expressed the opinion that fatty changes do not take place to any great extent in this milky condition of the pia-arachnoid, but an opposite opinion is held by Ziegler.

Whatever may be the actual state of matters in the pia-arachnoid, I feel assured that these conditions met with in the choroid plexuses, and fairly comparable to the milky opacities of the pia-arachnoid, are associated with distinct fatty changes in the endothelial cells, often of a widespread character.

(*c*) Only on one occasion have I seen an example of what W. F. Robertson[23] calls "vitreous degeneration." This author has described the condition as affecting the endothelium on the surface of the dura and lining the perivascular canals of its substance. "This retrograde change," he adds, "though common and important in the dura mater, is somewhat rare in the pia-arachnoid."

In the early stages there may be vacuolation of the cell

plate, but the change is essentially in the nucleus, which swells up and becomes vacuolated. These vacuoles, at first small and few, gradually increase in size and number, and run together, converting the nucleus into a collection of irregular cavities, staining faintly with hæmatoxylin. These vacuoles are, to begin with, separated by thin strands of granular protoplasm, staining more deeply with hæmatoxylin. Eventually, however, even these filaments disappear, and a large distorted form results, of a homogeneous glassy appearance, and staining very faintly with hæmatoxylin. This vitreous degeneration is altogether different from the hyaline change which occurs in these same cells. In the first place, it is principally nuclear, and, secondly, the homogeneous substance produced does not stain with eosine. It is, moreover, not a fatty condition, as osmic acid causes no blackening of the vacuoles or the completed homogeneous mass.

(*d*) Pigmentary degeneration of the endothelial cells is by no means a rare condition. It consists in an infiltration of the cell plate by numerous little globules of a bright yellow colour. The pigment, at first small in quantity, is gradually added to until no unaltered protoplasm remains, and in this way a very considerable increase in the size of the cell may result. This is undoubtedly a morbid change, as evidenced by the fact that almost every cell in a considerable area may be pigmented. Normally cells with pigment do exist, but they are always few in number and far between. It is, however, highly probable, as Robertson[4] suggests for this degenerative process in the pia-arachnoid, that "at the same time it is a change that may have a physiological basis in the normal pigment cells, just as in pigmentary degeneration of nerve cells the granules that replace the protoplasm are merely an increase in a normal element."

Foreign Elements in the Spaces of the Choroid Plexus.—Before passing on to a consideration of the changes in the vessels, it will be convenient to describe here some foreign elements commonly found in the spaces of the choroid plexus.

(*a*) Red blood corpuscles and granular *débris* resulting

from their disintegration are frequently found. The occurrence of the former is, I feel sure, not altogether unartificial, for extravasated blood cells are more frequently met with in preparations which were frozen in dextrine and cut than in those firmly embedded in celloidin.

(*b*) Hæmatoidin granules are often present, especially in cases of senile insanity. They are always discovered around vessels, in the spaces just beyond the adventitia. The arteriole surrounded by them may be thickened or even occluded, and their occurrence must indicate a rupture near at hand in the course of the vessel. This pigment is of a dark coppery or old-gold colour, and, moreover, is almost never diffuse, but usually is found in little heaps or aggregations.

I cannot help thinking that these two conditions, viz., pigmentary degeneration of the endothelial cells and the occurrence of hæmatoidin granules, are closely related to one another. They are frequently associated, and while pigmentary degeneration may occur in the other insanities, it is specially common in that known as senile.

The endothelial cells throughout the body are remarkable for their active phagocytic properties, and on several occasions they were observed playing such a *rôle* in the spaces around a vessel. As a rule the hæmatoidin granules are darker in colour than the pigment found in the interior of degenerated cells. But to this rule there are numerous exceptions, and in many cases it is difficult to say whether we are dealing with hæmatoidin granules or cell pigment. From these facts, then, I think we are warranted in concluding that, in senile insanity at least, a great part of the apparent pigmentary degeneration is due to the endothelial cells having englobed these hæmatoidin granules, and in some cases further altered them. That the two pigments are identical with, or closely related to, one another and the blood pigment itself, receives confirmation from photography. Blood offers considerable resistance to the actinic rays, and in the photographic negative is represented by thin, clear areas. The same occurs when hæmatoidin granules or pigmented cells are photographed.

(*e*) *Hyaline-fibroid Change in the Vessels.*

This pathological alteration may be found in all the vessels—arteries, capillaries, and veins, but seems to affect mainly the two former. Of the arteries, the smaller ones and the arterioles show this degeneration to the greatest extent. The adventitia alone, or the intima and media together, may be affected, but by far the most common condition is to find the whole three coats involved.

Hyaline Degeneration of the Adventitia.—This consists in a homogeneous thickening of the longitudinally running fibrous tissue. The swelling may be slight or considerable, stains a faint pink with eosine, and as a rule is devoid of granularity. In the smallest arterioles, with only one layer of muscular cells, and in which the adventitia in the normal condition is made out with difficulty and appears as little more than a fine line, the diseased adventitia may form a swelling two or three times the thickness of the original wall. Where two arterioles with thickened adventitiæ lie alongside one another, it may still be possible to make out the presence of a lymph space between them lined with elongated endothelial cells. In other cases, however, where the swelling has been more considerable, this space becomes quite obliterated by the blending of the two adventitiæ, while here and there an elongated cell shows up to indicate where a channel or sinus has been. This thickening is often irregular, and frequently leads to considerable distortions of the vessels. When the hyaline swelling is regular there is very little alteration in the calibre of the vessel, but irregular and nodular swellings invariably lead to serious narrowing of the vessel tubes. The adventitia never becomes much thickened without the muscular coat showing similar degenerative changes.

Hyaline Degeneration of the Muscular Coat.—The muscular coat, as a rule, is only involved secondarily to a hyaline degeneration of the intima, the explanation of this being that the media derives its nourishment from the interior of the vessel, and not from without as in the case of the adventitia. This sequence of events may be traced

very frequently, though now and then the media appears to degenerate without any previous hyaline thickening of the intima. In such cases, however, it is frequently found that, in the adjoining parts of the same vessel or in neighbouring vessels, the intima is thickened and hyaline. Probably in all cases of hyaline degeneration of the media, there is first of all a similar change in the intima. In cases where such a change cannot be demonstrated, we are warranted in assuming the presence of a chemical alteration in the constitution of the connective tissue fibres. Such chemical change in all probability precedes the more evident structural one, and this is all that is required to interfere with the normal process of osmosis. A chemical barrier of hyaline structure is interposed between the media and its nutritive supply, and thus is brought about a starvation of the muscular fibres leading to a subsequent degeneration.

The degeneration consists, firstly, in a swelling up of the muscular fibres, and in eosine and hæmatoxylin preparations the nucleus is well stained and is surrounded by clear protoplasm with no affinity for eosine. Then the nucleus gradually loses its tendency to stain deeply with hæmatoxylin, while the muscular protoplasm shows an increased affinity for eosine. Frequently, instead of this homogeneous layer, a finely granular appearance is produced from the presence of numerous eosinophile granules in the muscle cell-plates, and this may occur before total disappearance of the nucleus. In osmic acid preparations, it is found that some of these granules are of a fatty nature, for they become distinctly darkened by this reagent.

Hyaline Degeneration of the Intima. — The intima appears normally in the arterioles, when cut longitudinally, as a thin band of tissue covered by endothelium, between the lumen of the vessel and the muscular layer; while close to the latter can be made out, even in the smallest arterioles, a delicate elastic lamina.

The intima rarely becomes so much thickened as the adventitia. Such thickening, when it occurs, consists of a homogeneous hyaline mass, which is very irregular on its external surface, dipping down into the degenerated muscu-

lar layer, and pushing the elastic lamina before it. In no case, so far as I have seen, does the elastic lamina itself undergo this hyaline change. When present, it continues to separate the intima from the media, dipping down into the latter, and forming in it numerous loops in order to fulfil its purpose. Wherever the elastic lamina projects into the media, no muscle cells can be seen, though between the loops the muscle may retain its affinity for nuclear stain, and therefore its vitality. Into places where the muscle appears healthy, the elastic lamina and thickened intima have made no inroads. Therefore it may be assumed that the presence of points of diminished resistance has something to do with the excursions of the elastic layer.

In the intima this hyaline tissue may be invaded by cells and be converted into fibrous tissue, so as to present all the appearances of an endarteritis obliterans. In some cases the cellular infiltration is very abundant, while in others, again, remarkably few cells are seen, only an odd one here and there showing up between the thick fibrous tissue fibres. When the hyaline material has been replaced by new-formed fibrous tissue, the arterioles show a narrowed and irregular lumen. This narrowing and distortion in some cases is extreme, and actual occlusion may be brought about. The latter condition is, however, sometimes due to thrombosis occurring in the altered vessel, and the thrombus itself eventually acquires a homogeneous hyaline appearance. Lining the wall of such an endarteritic vessel, a single layer of endothelial cells is found next the lumen, and between this and a more or less degenerated muscular coat is a certain amount of fibrous tissue, with round, oval, or spindle cells between the fibres. The endothelium is frequently raised up from the thickened intima, leaving a space which contains no formed elements. Such a separation may also occur between a thickened intima and degenerated muscular coat, and likewise between a diseased media and adventitia. W. F. Robertson[5] thinks that these spaces are not altogether artificial, though perhaps exaggerated by bichromate hardening. They are filled with a clear fluid in which Robertson has occasionally seen a few leucocytes.

Mixed up with this fibrous tissue, especially when the thickening of the intima is considerable, may be seen elastic fibres or bundles. In transverse or longitudinal sections it is possible to make out two, three, or more elastic laminæ, separated by fibrous tissue and cells. In other cases it looks almost as though the entire thickening was due to a hypertrophy of the elastic lamina, with only a few cellular elements separating the different layers. The wavy course of the elastic lamina becomes still more wavy and, so far as I can see, shows no tendency to become straightened out, as Carl V. Rad [32] has found it in syphilitic endarteritis. It is often possible to make out that the different layers of elastic tissue become continuous with one another, forming eventually, mayhap only at one spot, the single normal elastic lamina. The secondary laminæ present the same exaggerated sinuosity of the original one, but are thinner, though by no means invariably so.

The elastic lamina is described by Schäfer as formed of elastic tissue, which occurs in longitudinal networks of fibres, consisting of one or more layers of different degrees of closeness. Under normal conditions, in any of the arteries in the choroid plexus, the elastic lamina appears as if composed of a single layer of elastic tissue; this layer varying in thickness with that of the artery. Still, it may be possible that, even here, the elastic lamina is made up of two or three layers, though such cannot be demonstrated. That the extra elastic laminæ owe their origin to a bursting asunder of these layers by new-formed tissue, as held by Carl V. Rad and Rumpf,[33] seems not at all unlikely. Thus, two elastic laminæ are explained by the division of the primary layer, and three by a further division of the secondary lamina, and so on. But it seems to me that the process, though perhaps in part, is not altogether a mechanical one, for there is no doubt that in many cases the elastic lamina is very distinctly hypertrophied. It becomes thickened and lengthened, so that its normal sinuosity is much increased. This great sinuosity, moreover, is not produced after death, for there is no associated distortion of the intima or endothelium. If the elastic lamina did not play an active *rôle*,

the thickened intima would tend to obliterate the normal winding, making it in parts quite straight, as Carl V. Rad describes in the basilar arteries of the brain. Such, however, is not the case as found in the smaller vessels of the choroid plexus. Moreover, this view of Rumpf and Carl V. Rad does not explain the fact that in some cases the new-formed elastic lamina lies immediately under the endothelium.

In reference to this condition Heubner[34] advances quite a different explanation: "when the endothelium is no longer caused to proliferate cells from syphilitic irritation, its normal function begins, which it possessed at the time when the artery became thickened; it forms a fenestrated membrane over the new-formed tissue, as it formed the same in young organisms over the muscular layer." This further explanation of Heubner has more lately been supported by Löwenfeld,[35] and appears to me to be in accordance with the facts. Frequently, as already mentioned, a layer of elastic tissue may be seen immediately under the endothelium, and separated a considerable distance by new-formed tissue from the original elastic lamina. Moreover, though sometimes the continuity of this superficial layer with the deeper one can be made out, in other cases no such connection can be traced. The only way to account for its presence, then, is to assume, as Heubner does, that the endothelial cells may again become possessed of that power of forming elastic tissue which they had in the embryo. Though Heubner is only writing of syphilitic disease of the vessels, there is no reason why we should not apply his arguments to the vessel change under consideration, more especially in the light of the opinion expressed by him in this same work, that "there are no certain histological criteria for deciding on the presence of syphilis." The above views of Heubner and Carl V. Rad, while explaining the increase of the elastic tissue in some, do not do so in all cases. There occurs now and then a very distinct hypertrophy of the fenestrated membrane with little or no proliferation of the endothelial cells, and Löwenfeld describes one such case. From a consideration of these facts, then,

I am forced to the conclusion that there must be some inherent vitality in the elastic lamina itself, and that under certain circumstances it is capable of proliferation and growth. At the same time this hypertrophy of the elastic lamina is not invariably associated with the hyaline-fibroid change. The fenestrated membrane may be broken through in parts or even be absent altogether.

Dilatations and Aneurisms of the Arterioles.—Narrowing and even occlusion of an artery or arteriole, as shown already, may be brought about by the hyaline change itself or by the subsequent reparative processes added thereto. But this is not the only alteration that may result. Sacculations and dilatations of the vessels, and even miliary aneurisms may occur; and, without doubt, are closely related to and dependent on hyaline degeneration in the vessel coats. This condition of dilatation has been called by Löwenfeld "die Rosenkranzform des Muscularisrohres," from the resemblance of the affected vessel to a rosary, and is found chiefly in the smaller arterioles. In such an arteriole there is throughout a mild degree of degeneration and hyaline thickening of the intima, and this, though slight, is sufficient to interfere with the nutrition of the muscular layer, as shown by the loss of nuclear staining and the presence of eosinophile granules in the muscle protoplasm. Where this degeneration of the media is most marked the vessel yields to the pressure of the blood, leading to the formation of a little fusiform dilatation, and the presence of several of these dilatations gives the appearance of a rosary. Moreover, in those places where sacculation has occurred, it may be seen that the thickening of the adventitia —almost invariably hyaline—is less marked, while at the points where the vessel presents a normal or narrowed calibre this thickening is more extreme. In other cases a nodular swelling of the adventitia may produce a localised fusiform thickening of the vessel, and such may be mistaken for a dilatation or an aneurism. But with this condition there is no increase in the size of the lumen; in fact, a narrowing as a rule occurs. These are evidently what Kromayer [36] has described as "pseudo-aneurisms."

On reviewing the pathological appearances of this hyaline-fibroid change, we may conclude that the greater the amount of hyaline material formed in the intima, the greater is the degeneration of the muscular coat, and the liability to dilatation. On the other hand, however, the facts show that the liability to dilatation is not in direct ratio to the hyaline thickening. Such hyaline material may become so thick and dense—this result may be attained by the transformation of the hyaline into fibrous tissue—as to compensate for the loss of the muscular coat, and prevent the occurrence of dilatation. This thickening, when carried beyond a certain point, leads to narrowing and even occlusion of the vessels; in other cases, again, pseudo-aneurisms are formed. A very large proportion of the cases examined showed evidence of chronic Bright's disease, and the increased blood pressure in this condition must have been an important factor in the production of dilatations.

While the small fusiform sacculation is the type of dilatation more commonly present, distinct miliary aneurisms, similar to those met with in the meninges, are found. In the meninges this condition most frequently exists in senile cases, and was found present by W. F. Robertson in five out of twenty-five such cases examined. I only, however, came across about half that number in the choroid plexus.

These aneurisms usually occur in the small arterioles with only a single layer of muscular cells, and are microscopic in size. The greater part of the aneurismal wall is composed of a dense layer of fibrous tissue, which is continuous with the hyaline media and thickened intima of the arteriole entering and leaving it. Scattered through this thick fibrous tissue are a few cells round and spindle-shaped, but nothing is seen to suggest the presence of muscular tissue. The inner surface of the sac is lined by a layer of endothelium. The "Rosenkranzform" dilatation must be considered as a step in the formation of a miliary aneurism, and rosary like arterioles are always present when an aneurism is found. Following on this the development of such an aneurism must have been

gradual, allowing sufficient time for a reparative process to take place in its wall. This would be brought about, first of all, by the proliferated endothelial cells invading the hyaline mass, till a condition of endarteritis would be produced. But the growth of the aneurism would not be arrested here. So long as the tissue was incompletely formed dilatation would go on, and would only cease with the complete conversion of the granulation into fibrous tissue. These miliary aneurisms are true aneurisms, and not merely, as Eppinger [37] holds, examples of ectasis or dilatation in which all the coats of the vessel are present.

Charcot and Bouchard [38] say that "miliary aneurisms are the result of a diffuse periarteritis, the first stage of which is characterised by a multiplication of nuclei in the outer coat of the vessel. This inflammatory condition causes atrophy of the muscular layer, and so renders the vessel wall liable to yield to the blood pressure. In the later stages the excess of nuclei disappear, and the vessel becomes thickened and fibrous. It is in the early stage alone that it tends to dilate."

Robertson and Löwenfeld are of opinion that this view of Charcot and Bouchard cannot be borne out. No more can I agree with it, for around the "rosary form" of artery —undoubtedly the precursor of the miliary aneurism—there is always a complete absence of periarteritis.

So far as my experience goes, vascularisation of either the hyaline or fibrous thickenings does not occur to any extent. Newly formed capillaries are not infrequently found in the thickened adventitia, but never have I seen new-formed vessels in the thickened intima of the arteries and arterioles found in the choroid plexus.

Such narrowing and obstruction of vessels always lead to the compensatory formation of new vessels or capillaries, and such in all probability exist here. But on this point one cannot dogmatise, for the vessels of the plexus are everywhere very numerous, and unless in the villi, present no regular sort of arrangement. Thus aberrations from the normal type could not easily be detected, and, moreover,

there is nothing in the minute structure to distinguish the original capillaries from those more newly formed.

Hæmorrhages are occasionally found, and more frequently hæmatoidin granules. The former are never considerable and occur in cases presenting well marked hyaline changes. These are the cases, besides, in which new-formation of vessels would be most likely to occur, and in all probability a rupture of one of these accounts in many instances for the hæmorrhage.

Hyaline Degeneration of Veins and Capillaries.—This hyaline change may also attack the veins. Their fibrous tissue walls become swollen up and eventually replaced by a layer of hyaline material. This is frequently associated with a well-marked hyaline degeneration of the connective tissue fibres in the neighbourhood of the vein. The thickening is never very extensive, but the spaces so frequently seen in their walls become obliterated. More serious are the results of this condition when the venules and capillaries are affected. Oeller[39] describes a preliminary proliferation of the endothelial cells subsequent to which the hyaline thickening occurs. Whether such is really the case I cannot say, but there is no doubt that an increase of the endothelial cells is frequently found along with the hyaline thickening; and these two conditions very often lead to obliteration of the venules and capillaries. Probably in some cases, though by no means in the majority, this obliteration is actually brought about by thrombi forming in the altered vessel, these thrombi after a time likewise assuming a hyaline appearance. Later on the hyaline cords may lose their homogeneous character and become distinctly fibrillated. Dilatation of hyaline capillaries is said by W. F. Robertson to occur very rarely, and such I have seen on only a very few occasions.

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[*These illustrations have been kindly lent by the editors of the Journal of Mental Science.*]

EXPLANATION OF PHOTO-MICROGRAPHS.

Fig. 1.

Central part of glomus. (× 26). From a case of puerperal insanity. In the centre is shown the normal arrangement of large and distinct spaces, analogous to the "subarachnoid spaces," or "arachnoid cisterns." Numerous blood-vessels and concentric bodies are also present.

Fig. 2.

Glomus. (× 26). From a case of alcoholic insanity. Here is seen the normal proportion of blood-vessels. The walls of the arteries are thickened from hyaline degeneration. Observe how the fibrous tissue of the walls of the veins very quickly merges into the surrounding spongy tissue, in some cases the trabecular spaces coming quite close to the intima.

Fig. 3.

Irregular forms of hyaline concentric bodies, produced by the coalescence of several spheres. (× 120). From a case of puerperal insanity.

Fig. 4.

Development of a hyaline concentric body from a venule. (× 240). From a case of general paralysis. In centre of photo is seen a venule, the wall of which is enormously thickened from hyaline degeneration. The hyaline circle shows concentric markings, and the interior is packed with proliferated endothelial cells, likewise in a condition of hyaline degeneration.

Fig. 5.

Portion of a cyst of the choroid plexus. (× 140). From a case of general paralysis. To the left are seen the greatly dilated spaces of the pia-arachnoid, lined by degenerated and degenerating endothelial cells. A few degenerated cells are floating in the fluid distending these spaces, and some of the connective tissue trabeculæ show the hyaline change. To the right of this open network, and gradually blending with it, is a dense tissue in which there has been very extensive proliferation of the endothelial cells lining the trabeculæ.

Fig. 6.

Transverse section of a hyaline arteriole. (× 240). From a case of senile insanity. The intima is greatly thickened, and amidst the fibrous tissue may be seen several layers of wavy elastic laminæ.

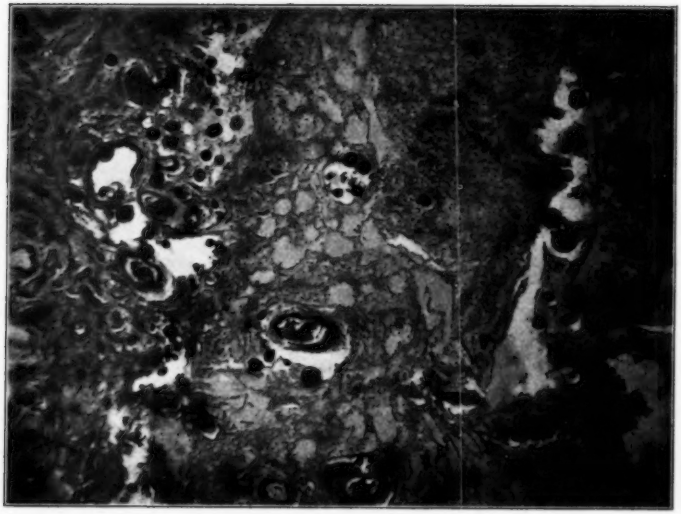

FIG. 1.

Central part of glomus, showing large and distinct spaces. Puerperal Insanity. (× 26.)

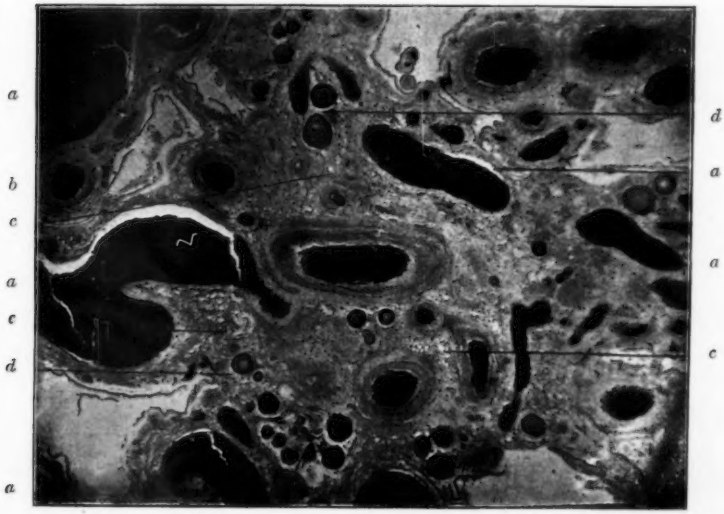

FIG. 2

Glomus showing usual distribution of veins. Alcoholic Insanity. (× 26.) *a*, Veins; *b*, Arteries; *c*, Open trabecular arrangement; *d*, Hyaline concentric bodies.

To illustrate Dr. FINDLAY'S Paper.

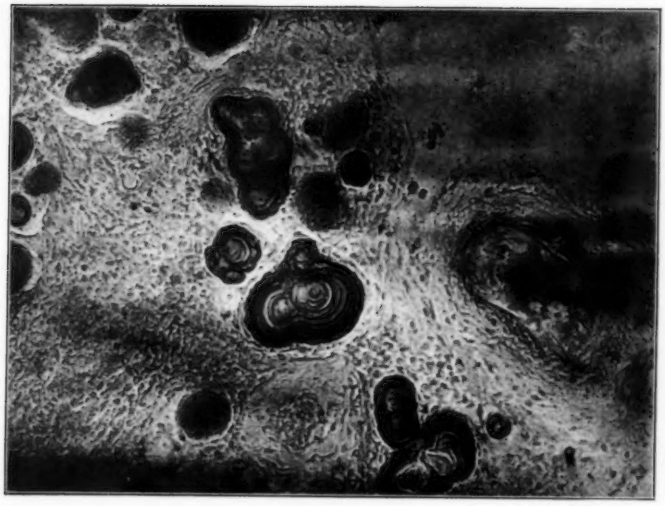

FIG. 3.
Irregular forms of hyaline concentric bodies. Puerperal Insanity. (× 120.)

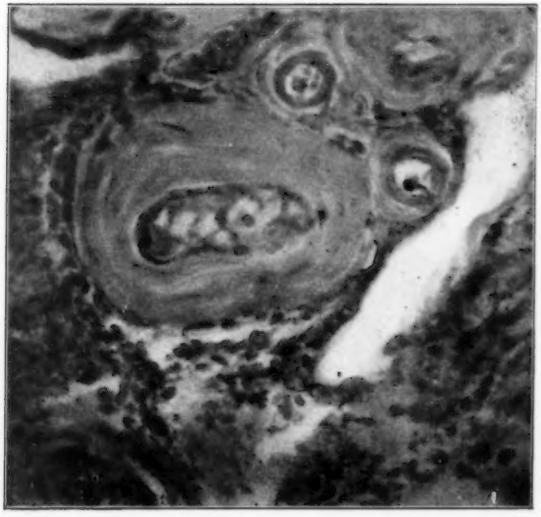

FIG. 4.
Development of hyaline concentric bodies. Wall of venule enormously thickened from hyaline degeneration, proliferation of the endothelial cells. General Paralysis. (× 240.)

To illustrate Dr. FINDLAY'S Paper.

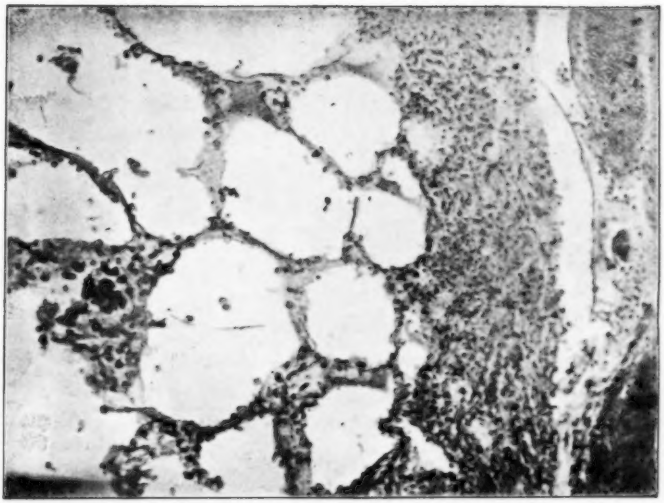

FIG. 5.
Cyst of choroid plexus.

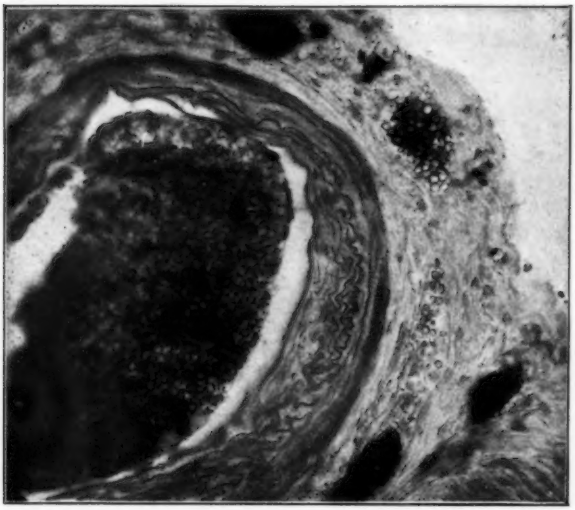

FIG. 6.
Section of arteriole, showing several layers of elastic laminæ.
To illustrate Dr. FINDLAY's Paper.

Critical Digest.

NORMAL AND PATHOLOGICAL HISTOLOGY OF THE NERVE-CELL.

BY W. FORD ROBERTSON, M.D.,

Pathologist to the Scottish Asylums.

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IV. *Addendum upon physiological and pathological deductions.*

THE purpose of this digest is to present a systematic account of the more important observations that have been made during the last five years upon the normal structure of the nerve-cell and upon the morbid changes to which it is subject. Our knowledge of the normal histology and physiology of the neuron as it stood in 1893 was summarised by Professor Schäfer (471) in his presidential address to the Neurological Society delivered in that year and afterwards printed in this journal. In the same year, Aldren Turner (490) and Tanzi (499) published critical digests which dealt with the facts and inductions derived from the study of the nervous system with the aid of Golgi's method. These papers related mainly to the external form of the normal nerve-cell, the course of its ramifications, and its anatomical and physiological relations to other nerve-cells. Since that time, the advances that have been made in our knowledge respecting these points are by no means great. On the other hand, the essentially different subject to which I limit the present digest—the internal structure of the nerve-cell and its alterations in morbid conditions—is one in regard to which there has been an activity of research and a rapidity of progress, probably unparalleled in the whole history of neurological science. As yet the great mass of the observations that have been made are recorded only in papers in the various medical journals, and it will therefore probably be generally conceded that there is need at the present time for some such systematic epitome of them as it is here endeavoured to give. It should be stated, however, that the work that has been done has twice been the

subject of critical review on the Continent, viz., by Lugaro (242) in 1896 and by Marinesco (314) in 1897.

In so far as has been practicable, I have studied the original paper to which reference is made. When this has been inaccessible to me—and it has rarely been so except in the case of some papers of secondary importance—I have contented myself with the perusal of the abstracts in such journals as the *Rivista di Patologia Nervosa e Mentale*, *Neurologisches Centralblatt* and *Revue Neurologique*. Owing to the very large number of papers requiring notice, it has been impossible to give the title of all of them in the bibliography, but it is trusted that the reference in the text will in every instance be sufficient to indicate the subject. I have endeavoured to supply a complete review of the work recorded from 1894 to 1898, but I can scarcely hope that I have not omitted to notice some observations of importance. A practically complete classified list of the neurological papers published since 1895 will be found in the very useful *Bibliographischer Semesterbericht*, which is now being issued by Dr. G. Buschan (Fischer, Jena).

In the succeeding pages it will be necessary from time to time to make mention of the histological *technique* employed by the various observers. It will, therefore, probably conduce to clearness if at the outset I give a brief general account of this subject in its relation to the study of the nerve-cell. Most of the methods now in use will be found described in detail in the recent text-books upon histological *technique*, such as those of Bolles Lee and Pollack. With regard to the fixation of nervous tissues in which it is intended to study the nerve-cells, the great weight of authoritative opinion is at present undoubtedly in favour of the use of corrosive sublimate after Heidenhain's method (G. Mann (331), Lugaro, Giuseppe Levi, Lenhossék, Dotto e Pusateri). There are still many, however, who continue to use 96 per cent. alcohol, as originally advocated by Nissl. Another fixing agent that has lately come to be very largely used in the neurological laboratory is formaldehyde, which is sold as a 40 per cent. solution in water under the name of formalin. The original methylene blue staining method of

Nissl (358-362), to the introduction of which is largely due the impetus that has been given to the study of the nerve-cell, has been extensively used by many observers. It has, however, been essentially modified in the hands of some of the best authorities on nerve-cell histology, although still commonly referred to by them as "Nissl's method." Nissl proscribed paraffin embedding. Such high authorities as Lugaro, van Gehuchten, Marinesco and Giuseppe Levi, as well as numerous others, have, however, constantly employed it in their work. Those who have in this respect departed from the *technique* advocated by Nissl have also as a rule substituted another stain for the methylene blue patent B, those most in favour being toluidin blue and thionine. Numerous other staining methods have been employed, chiefly for the demonstration of some particular histological point. Thus, Rosin (446) and Giuseppe Levi have used the Ehrlich-Biondi reagent for the determination of the acidophile and basophile properties of the different constituents of the nerve-cell. Lugaro has specially advocated the use of Delafield's hæmatoxylin and of Heidenhain's iron-hæmatoxylin method for the demonstration of the primitive fibrils of the nerve-cell protoplasm. Elective staining methods for these fibrils have been described by Becker, Held and Bethe. Ehrlich's *intravitam* methylene blue method, which is of much earlier origin than Nissl's method, has also been very extensively used during the period under review, and has been variously modified by numerous workers, among whom may specially be mentioned Dogiel, Semi Meyer, Bethe and Donaggio. Lastly, the chrome-silver and sublimate methods of Golgi have been largely used, not only for the study of the normal cell, but also for the investigation of its pathological changes. Innumerable modifications have been described, some of them undoubtedly of considerable importance. Foremost among these is, beyond question, Cox's modification of the sublimate method, which, according to Lugaro and many other authorities, is the most trustworthy method of this class for the study of pathological changes. Improved processes of blackening the mercurial deposit have added largely to the

value of the sublimate methods. Cox recommended the use of sodium carbonate for this purpose, G. Mirto (340) has specially advocated lithium carbonate, and Donaggio (101) sodium or potassium hydrate. The last-mentioned method was afterwards independently described by Bevan Lewis (273).

I. Normal Structure of the Nerve-cell.

(1) *Terminology.*

The term *neuron* is now in general use to denote the whole nerve-cell, including its processes. The suggestion of Schäfer (471) that it should be employed for the axis-cylinder process has not been adopted. Kölliker (229) has objected to Waldeyer's use of the word *neuron* upon etymological grounds and has advocated instead the terms *nervenbäumchen*, *neurodendron* or *neurodendridion*, which, however, have been very little employed by others. Schäfer proposed that the term *nerve-cell* should be used in the same wide sense as *neuron*, and in the writings of most authorities this signification is now generally given to it.

Taking the motor cell of the anterior horn of the spinal cord as the type, we may enumerate the various constituent parts of the nerve-cell as follows:—The nucleus and nucleolus; the Nissl-bodies; the achromatic substance, composing the greater portion of the cell-body, the protoplasmic processes and their gemmulæ and also the axis-cylinder process, its collaterals and terminal arborisations; the pigment; and lastly, the pericellular and endocellular networks of Golgi, granting that they exist as distinct elements. For some of these constituents of the nerve-cell a large number of different terms have been employed by recent writers. The Nissl-bodies have been referred to by Nissl (363) himself as the *visible, formed*, or *stainable part of the protoplasm*, *the chromatic substance* (Marinesco, Lugaro and others), *the chromophile part of the cytoplasm* (Levi and others), *the chromatophile elements* (Lugaro, Marinesco, van Gehuchten and others), *the chromophilic particles* (Berkley), *the basophile constituent* (Eve), *the*

tigroid substance (Lenhossék), *the collagenous substance* (van Gieson), &c. The employment of the term *chromatic*, which has been very general, has led many into the belief that the Nissl-bodies are regarded as composed of chromatin. Some writers have indeed maintained this view, but its erroneousness has been fully proved. *Chromophile (part, substance, or elements)* is the term that is probably least open to objection, and it is one that has recently been largely used. It has, however, been employed by Nissl in a different sense, namely, to denote that condition of the nerve-cell which is characterised by abnormally deep staining with his method (a condition which is now generally regarded as due to the action of the fixing agent), and by Flesch to designate nerve-cells that have a very strong affinity for basic dyes (such as the small, dark cells of the spinal ganglia), in contradistinction to those that have not this character, which he termed *chromophobe* cells. These early uses of the word have now, however, been practically abandoned. *Basophile constituent* must be rejected, because, as Nissl and Levi have shown, this substance has only relative basophile properties. Nissl (363) has objected to the terms *granules* and *granular substance* as being in a large measure false.

There is, unfortunately, considerable confusion regarding the terminology of that portion of the nerve-cell which is not coloured by Nissl's staining process, arising chiefly from the difference of opinion that has existed as to its essential structure. The term *achromatic substance* is that which has undoubtedly been most largely employed. Many writers now use the expression *fundamental substance* synonymously with it. Nissl (363) used the terms *invisible, not formed* and *unstainable* substance upon grounds that are now known to be erroneous. In 1896 Marinesco (305) applied the term *trophoplasm* to the achromatic part of the nerve-cell, believing that this part presides over the nutrition of the neuron. The chromatic part he called *kinetoplasm*. Lugaro (242) has pointed out certain objections to these terms. Marinesco in a later paper (322) gives a fuller exposition of his use of them. Recognising with many

other authorities that the achromatic part of the protoplasm is composed of two different elements, he divides it into—(1) *the fundamental achromatic substance* and (2) *the organised fibrillar achromatic substance*. He therefore, it will be seen, limits the meaning of the term *fundamental substance*. He now restricts the term *trophoplasm* to this non-organised portion and calls the fibrillar substance the *spongioplasm*. This terminology proposed by Marinesco certainly deserves the most careful consideration. Its general adoption, if justified by histological and physiological facts, would undoubtedly be very useful. It is to be noted that Gowers (182) has recently employed the terms *kinetoplasm* and *spongioplasm* in quite a different way from the distinguished neurologist of Bucharest.

The protoplasmic processes are also referred to as the *dendrites* (His), *dendrons* (Schäfer) and *dendritic processes*. The gemmulæ of the protoplasmic processes have been variously referred to as the *spines, thorns, spinous processes, lateral buds, pyriform processes*, &c. Synonymously with *axis-cylinder process* the terms *nervous process* (Waldeyer), *nervous prolongation* (Lugaro and others) *neurite, neuraxon*, and *axon* (Foster (146) and others) have frequently been employed. Kölliker (229) made certain distinctions in the use of these terms which have not been generally observed by others. He restricted the terms *nerve-fibre process, neuraxon* and *axon* to those processes that become axis-cylinders of medullated fibres, and the terms *nervous process* and *neuropodion* to those that run a short course and do not become true nerve-fibres. The term *neuroplasm* was given by Kölliker to the homogeneous interfibrillar substance of the axis-cylinder of nerve-fibres. It has been applied by Benda (51), Nissl (366) and Bühler (41) to certain elements that they distinguish in the cell-body, which, however, are not strictly identical (see Section I. (2)).

The term *neuropilema* or *neuropil* was applied by His to the dense trellis-work of fine fibrils (mostly collaterals) which occurs in the nerve-centres. Its use has lately been revived in the discussion of the special views of Apathy regarding the constitution of the nervous system.

Foster (146) has proposed that the cell-body should be called the *perikaryon*, and that the connection of one nerve-cell with another by means of a terminal arborisation applied to the cell-body or to the dendrites should be termed a *synapsis*.

(2) *Nissl-Bodies or Chromophile Elements.*

The progress that had been made in the study of the internal structure of the nerve-cell prior to the period under review, as well as up to the earlier part of this period, will be found recorded in such works as those of Lenhossék (277), Dejerine (122), van Gehuchten (168) and Kölliker (229) and also in a paper published by Nissl (364) in 1895. It was only with the introduction of Nissl's methylene blue method (358) in 1892 that the accurate study of the normal chromophile elements of the protoplasm may be said to have begun, and the paper about to be noticed was practically the first record of the results of such study, although Nissl had previously published two papers in which morbid appearances revealed by this method were described (Nos. 358 and 359).

In 1893 Nissl (360), selecting the cells of the spinal ganglia of man for special study, described them as presenting when stained by his methylene blue method a non-coloured fundamental substance, and coloured particles arranged concentrically around the nucleus and having filiform prolongations. These particles were of various sizes, round, oval, angular or irregular in shape. He maintained that the different degrees of affinity for basic stains presented by the nerve-cells, which had led Flesch to divide them into chromophile and chromophobe cells, were to be attributed to the opposite functional states of activity and repose, and not to the fact that they have a different chemical constitution and different functions as Flesch (151) had maintained. In the same year Rosin (446) recorded some observations upon the structure of nerve-cells made with the aid of Biondi's triple stain. He maintained that the body of the cell is composed of two substances which have different staining reactions, dependent, however, not

upon morphological but chemical differences. One of these substances he regarded as analagous to basophile granules in the sense of Ehrlich. K. Schaffer (463) pointed out that the cone of origin of the axis-cylinder process differs from those of the protoplasmic processes in being devoid of chromatic substance, an observation which it is now recognised had previously been made by Simarro.

In 1894 Nissl (361) adversely criticised Rosin's work. In another paper (363) he maintained that the so-called granules essentially represented the morphology of the cell, in opposition to the contention of Rosin that they were merely chemical formations resulting from the union of a basic dye with an acid substance in the protoplasm. He denied that they had basophile properties in the sense of Ehrlich, finding that they could be stained with acid as well as with basic dyes. He also gave a further description of the morphological characters of these bodies. Though they presented themselves in many forms and varied considerably in size, they preserved a fixed arrangement. They appeared as irregular particles, smooth or dentate fibres, spindles, wedges, stellate masses, &c. They were grouped together or placed in rows. In some cells they were united into a network. In fusiform cells they frequently formed blocks, which were applied one to either pole of the nucleus (nuclear caps). At the point of bifurcation of the large protoplasmic processes there was generally a triangular mass of chromatic substance (cone of bifurcation). In the same year G. Mann (330) gave a description of the structure of the nerve-cells of the cervical sympathetic ganglia of the rabbit. He described their Nissl-bodies as occurring in the form of numerous short, rod-shaped chromatin granules. He also stated that he had been able to demonstrate by his methyl blue and eosine method bodies which showed characteristic staining reactions, and which had not previously been described. They consisted of dumb-bell shaped elements placed side by side. There were from four to ten of these "bigeminal bodies" in each cell.

In 1895 Nissl (365) pointed out that the nerve-cells may be divided into two great groups in accordance with certain

morphological features. Those of the first group, which he called the somatochrome cells, have a distinct cell-body containing colourable particles. Those of the second group, which he termed karyochrome cells, have only a small cell-body containing no colourable particles. He further divided this group into the karyochrome cells proper and the cytochrome cells or granules. He described the various arrangements of the colourable substance in the somatochrome cells and based upon them a classification of these cells (see I. (10)). Nissl (364) in another paper, in which he reviewed the position of nerve-cell anatomy and pathology, maintained that the relation of the amount of the substance stainable with basic dyes to the amount of unstainable substance varies in cells of the same kind. This variability of the staining affinity of the cell he again attributed, in the case of certain kinds of cell at least, to differences in functional state. He believed, however, that the condition of chromophilia, or very deep diffuse staining of the nerve-cells, was artificially produced by the fixing reagent. In the same year Lugaro (238) gave a description of the chromatic substance of the nerve-cells of the cervical ganglia of the rabbit as seen in Nissl preparations. He maintained that it does not exist in the form of isolated particles, but is united into a sort of reticulum, or into a figure comparable to the lacunar cavities of a sponge, and that it is not homogeneous, but composed of various elements more or less intensely colourable. Lenhossék (277) described the Nissl-bodies in the cells of the anterior horn of the spinal cord as compact, large chromophile particles and granules distributed throughout the cell-body, and giving to it a peculiar tigroid aspect. He observed differences in the size and number of the particles in different animals. He maintained that the Nissl-bodies are not artificial products, and that they are not granules in the sense of Altmann. In the cells of the spinal ganglia of the ox he found these bodies to occur as very small granules. He could not find the arrangement of concentric layers described by Nissl in the cells of the human spinal ganglion, but only an indefinite differentiation of the particles into an external and an internal layer, the latter

being the denser; nor could he confirm the statement that the particles give off fine threads. Held (201) maintained that the Nissl-bodies are composed of three different elements, namely, minute granules, a homogeneous substance and vacuoles. He regarded all of them, however, as artificial products resulting from precipitation determined by the fixing fluid; they did not exist in the form of large masses in the living cell. He based this contention chiefly on the facts that they are not visible in the fresh state, only commencing to form on the addition of water or of fixing agents, and that their morphological characters vary with the fixative employed. He studied the chemical reactions of the Nissl-bodies, making the observation among many others that they are insoluble in mineral acids, acetic acid, warm alcohol, ether or chloroform, soluble in certain other reagents, such as ferrocyanide of potassium and caustic potash. He included them in the group of nucleo-albumins. Becker (38) described in the Nissl-bodies numerous granules, which he demonstrated by the vital injection of neutral red. He likened them to Ehrlich-Altmann granules, and believed that they play an active *rôle* in cellular metabolism. Benda (51) maintained that the structures in the body of the ganglion cells which stain with basic aniline dyes are neither Ehrlich's granules nor specially formed cell-substance, but the undifferentiated protoplasm, the neuroplasm, which is filled in different degrees with basophile granules, and that the neuroplasm is sharply separable from a differentiated fibrillar substance. Dogiel (117) studied the chromophile substance of the nerve-cells in preparations made by his modification of Ehrlich's methylene blue method. He found that it assumes different aspects according to the duration of the action of the stain upon the fresh tissue. At first it appears as fine particles, but later as little masses which give the cell a speckled character.

In 1896 Lugaro (239) contended that the chromatic part of the protoplasm represents an interfibrillar mass, and that the achromatic part is constituted by the thread-mass of Flemming. Thus Nissl's method gives only, as it were, the negative of the true structural configuration of the nerve-

cell. Early in the same year Nissl (366) published a paper containing a minute analysis and criticism of the views advanced by Benda. Ramon y Cajal (426) stated that, studying the distribution of the chromatic part of the cytoplasm, both in the phylogenetic series and in ontogenetic development, he was able to observe in it a differentiation, the principal phases of which are as follows:—(*a*) Granular chromatin diffusely distributed without formation of very apparent aggregations; (*b*) Formation of peripheral aggregations placed around a large perinuclear space; (*c*) Formation of perinuclear aggregations; (*d*) Extension of the chromatic aggregations throughout all the cell-body and moulding of fusiform figures parallel to the expansions. Marinesco (305) described the occasional occurrence of fusiform enlargements containing abundant chromatic filaments in the protoplasmic processes of the motor cells of the spinal cord. Lugaro's important review of the position of nerve-cell pathology (242) in 1896, already alluded to, contains some remarks upon Held's views, which deserve quotation here. Lugaro thinks that Held's hypothesis that the figures obtained with the method of Nissl are artificial products due to a precipitation determined by the fixing agent, even if correct, does not in the least diminish the value of the pathological changes observed in the nerve-cell. Every microscopic figure is an artificial product, an image symbolic of certain morphological conditions; if this product is constant, and presents itself in healthy and pathological tissues in a different form constant for each, the different reaction has the value of an exact indication of the pathological alteration. With Held's assertion that the morphological picture varies with the fixative employed he cannot agree, finding that those fixatives, the superiority of which is now recognised, such as 96 per cent. alcohol, formalin and sublimate, give along with the method of Nissl the same structural figures. In the same year Lugaro (244) gave a minute description of the arrangement of the chromatic substance in the different types of nerve-cell in the posterior root-ganglion of the dog (see I. (13)). Juliusburger (220) maintained views regarding the composition of the Nissl-bodies

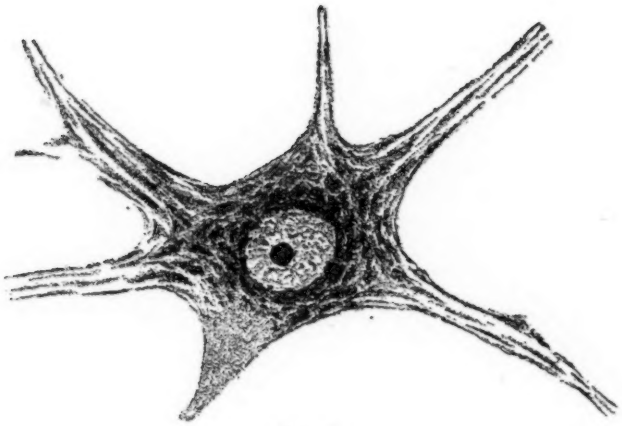

FIG. 1.

Cell of anterior horn of spinal cord of normal rabbit. Sublimate. Thionin. (Lugaro 250.)

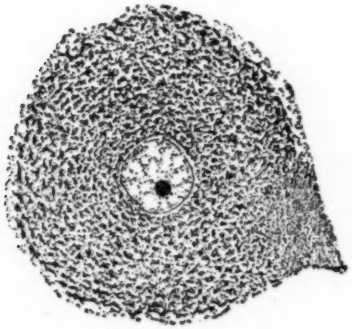

FIG. 2

Cell of spinal ganglion of normal dog. Lugaro's first type. Sublimate. Thionin. (Lugaro 244.)

practically identical with those of Benda. Eve (136) recorded observations upon the arrangement, development and chemical reactions of the "basophile particles," more especially in the cervical sympathetic ganglia of the rabbit. He found that these particles are insoluble in weak sodium chloride solution, but soluble in very weak solutions of caustic soda and acetic acid.

In 1897 Ramon y Cajal (431) gave a minute description of the chromatic elements of the cells of the spinal cord. He stated that the orientation of the chromatic corpuscles is more or less parallel to the outline of the motor-cell, while in the commissural cell it corresponds to the direction of the protoplasmic prolongations. The corpuscles are studded with little projections which penetrate between the trabeculæ of the achromatic substance; they are not homogeneous, but present numerous vacuoles in their interior. There probably exist in them also granules which have the staining reactions of chromatin. From four to six prolongations extend from each chromatophile body, by means of which it places itself in relation with other chromatophile bodies and with the cellular membrane. In the large and medium cells there are two kinds of chromatic elements. One is large, of polygonal form, and sends out prolongations; the other is small, rounded or irregular in form, and is placed at a nodal point of the reticulum of the spongioplasm. Early in this year (1897) there was published the second edition of van Gehuchten's *Le Système Nerveux de l'Homme* (168), in which there will be found a very full and clear description of the chromatic substance of the nerve-cell protoplasm in accordance with the observations made up to that time. In this year, also, Giuseppe Levi (262-263) published an account of his observations upon the comparative histology of nerve-cells. These researches, which extended throughout every class of vertebrate animal excepting birds, have resulted in what is beyond question one of the most important contributions that has yet been made to our knowledge of nerve-cell anatomy. It is impossible in a digest like this to give an adequate idea of the wealth of valuable details regarding the special structural features of the nerve-

cells in different animals that this observer has described, and in this sub-section I can only indicate a few of his conclusions regarding "the chromophile part of the cytoplasm of the somatochrome cells." He draws attention to its strong affinity for thionin, a dye which has not distinctly basic characters like methyl-green. He finds that with Biondi's method it is stained, though not intensely, with the acid colour and not with the basic. Therefore it has only weak basophile properties. He finds that the forms assumed by this substance in different animals are very various. It may appear as powdery granules, as more or less large granules, as threads, but more often as masses (*zolle*). Its fine structure in preparations fixed in sublimate is always granular. In different cells of the same animal the chromophile substance preserves a certain uniformity of type. For example, in the guinea-pig the cells of the anterior horn and those of the spinal ganglia have both large isolated chromophile particles; in the dog and ox they contain small diffuse granules; in the dormouse dense spindles. He believes that he has been able to establish the fact that the chromophile substance is deposited in particles, which are the more minute the more voluminous is the cell, independently of the position the animal occupies in the zoological scale. Thus, in the large cells of the ox and in the giant-cells of petromyzon the chromophile substance is powdery, while in the guinea-pig, bat and dormouse its granules are aggregated into large and more or less dense masses. While, as a rule, the chromophile particles are traversed in every direction by the fibrils of the achromatic substance, in certain cases (petromyzon) these two constituents are completely separated from each other. R. A. Fleming (145) has given a good *résumé* of the various views advanced up to this date regarding the nature of the chromatic substance. He mentions that Halliburton and Siegfried (like Held) consider that it is a nucleo-albumin. In the *Rapport* upon the pathology of the nerve-cell which he presented to the International Congress of Medicine held at Moscow, Marinesco (314) gave a precise description of the chromatophile elements of the protoplasm and of their relation to

the achromatic fibrillar portion. He stated that these elements, as seen in the large cells of the spinal cord, are disposed concentrically around the nucleus and prefer a polygonal form. The further they are placed from the centre the more elongated do they become, and in the protoplasmic prolongations take a fusiform aspect, their long axis being parallel to that of the prolongations. They are absent from the axis-cylinder process. They give to the cells of the anterior horn a spotted appearance like that of the skin of the tiger. Examined with very high powers, these chromatophile elements appear composed of elementary granules agglutinated by a pale achromatic substance. Van Gehucten (169), in a paper which was likewise brought before the International Congress of Medicine held at Moscow, gives a very minute description of the chromatic substance of the cells of the cord and posterior root ganglia. He regards its elements as forming in the motor-cells of the cord an incrustation upon the nodal points and trabeculæ of the achromatic network. The greater this incrustation becomes the smaller must be the spaces of the network. If it involves several neighbouring trabeculæ and nodal points, there is produced the structure of a chromatic block. Such a chromatic block does not present any regular contour, because fine incrusted trabeculæ extend from it on all sides. The chromatic substance in the cells of the spinal ganglia varies greatly in its form in different animals. It incrusts mostly the nodal points of an achromatic network and thus forms larger or smaller chromatophile granules. Held (202) published an account of further observations upon the chemical reactions of the Nissl-bodies, and maintained his previous opinion against the criticisms that had been made upon them. He found that if a fresh cord is fixed in alkaline alcohol the Nissl-bodies cannot be observed in the cells of the anterior horns. If a piece of cord fixed in this way is placed for some time in an acid solution the Nissl-bodies reappear. He maintained that the formation of these bodies depends upon the acid reaction assumed by the grey substance after death. In life the cells have an alkaline reaction and the constituents of the Nissl-bodies are in

solution. If a cord is examined immediately after death no Nissl-bodies can be seen, but they appear immediately on the addition of very dilute acetic acid.

In 1898 Marinesco (322) gave a very full description of the disposition of the chromatic elements in the cells of the sympathetic ganglia; and van Gehuchten and Nélis (176) described the arrangement of those in the various types of cell in the spinal ganglia of the rabbit. In this year there also appeared the important work of Bühler (41) upon the structure of the nerve-cells, a chapter of which is dedicated to the subject of the chromatic elements of the protoplasm. According to Levi (267), who has given a very full account of the contents of this paper, Bühler arrays himself with the majority of observers against the views of Held. He thinks that during metabolism in the nerve-cell there is formed an albuminoid which is soluble in normal salt solution and in alkalies, and is coagulated by the agents that usually coagulate albuminoids. It is distinguished, both in the fresh state and when coagulated, by a specific affinity for the basic aniline colours. It appears as spherules which are often united into more or less dense groups. When the functional processes of the cell are disturbed it either does not form or is formed in an abnormal fashion and dissolves. Timofeew (506) has noted that in birds (cells of spinal and sympathetic ganglia) the chromophile substance is specially abundant. Donaggio (105), in his most recent paper upon the reticulum which he demonstrates in the nerve-cells by means of his own modification of Ehrlich's methylene blue method, has suggested an interpretation of certain of the appearances presented which specially concerns the chromatic substance of the protoplasm. He finds that the reticulum (which corresponds to the spongioplasm of Marinesco) is, in the cell-body and initial portion of the large protoplasmic prolongations, invested by granules which stain more deeply than the threads of the reticulum. He thinks that these granules represent the chromatic substance of the protoplasm in its unaltered form and arrangement. Ewing (135) states that he is convinced "that the chromatic bodies are homogeneous in the natural state, that they make their appearance

in finely granular form shortly after death." He further maintains "that the chromatic structures in the cerebral, spinal and spinal ganglionic cells are always found in the form of a reticulum with nodal thickenings, which in the stichocromes reach a considerable volume, covering often several adjoining meshes of the network."

(3) *The Achromatic or Achromophile part of the Cytoplasm.*

It has been freely admitted by the other and more recent authorities that the researches of Flemming (139), of which an account was published in 1882, opened the modern epoch of the anatomy of the nerve-cell (Lugaro, 249, Nissl, 364). Flemming, using the iron hæmatoxylin method of Heidenhain and also staining with Delafield's hæmatoxylin, demonstrated the presence of short undulating fibrils in the cytoplasm of the cells of the spinal ganglia of mammals. He stated that they were continued into the colourable particles, and that they probably formed a network. In certain later writings the priority of Flemming in describing the primitive fibrils has been disputed upon erroneous grounds. Levi (262) has recently drawn attention to the matter and given a clear statement of the facts. He says:—"I think it opportune to point out an error into which those authors have fallen who assert that Flemming was not the first to demonstrate the presence of fibrils in the nerve-cells, but that he merely confirmed an old discovery of M. Schultze (*Stricker's Handbüch*, 1871, Bd. I.). As is known, this author believed that the fibrils are continued into the cell and converge in the manner of rays from the dendrites towards the nucleus without forming anastomoses, and are continued in the axis-cylinder, thus only traversing the cell. To what the fibrils seen by M. Schultze correspond I am not able to say with exactitude; it is presumable that a large part of the striæ described by him were formed by the chromophile particles of the dendrites, as Flemming believes; in any case, it is evident that this structure has nothing in common with that recently described in the nerve-cells, and to endeavour to identify it with any one only contributes to the creation of deplorable confusion."

In 1894 G. Mann (330), describing the sympathetic ganglia of the rabbit, stated that "the protoplasm of the cell consists of a ground substance with a great number of fibrils imbedded in it, which run in bundles and may be traced from one process past the nucleus to another process." He referred also to the existence of an interfibrillar ground substance in which the chromatin granules are embedded. In 1895 Held (201) maintained that, except at the origin of the axis-cylinder, the ground substance of the nerve-cell is never fibrillar. A fibrillar structure is simulated by the honeycomb appearance (vacuolation) caused by certain methods of fixation. Becker (38), by means of a method of his own, obtained an elective staining of the substance which remains unstained in preparations by Nissl's method. He stated that this substance is a direct continuation of the primitive fibrils of the axis-cylinder process into the cell-body and protoplasmic processes. Benda (51) also described a differentiated fibrillar substance in the cell-body and processes. Dehler (106) observed in the cells of the sympathetic of the frog elongated granules, which formed a fibrillar network similar to that described by Flemming. But he found transitions between the fibrils and the chromatic substance, and therefore believed that they were not distinct structures. Lenhossék (277) denied that the ground substance of the nerve-cells contains fibrils, attributing to it a spongy structure. Dogiel (117), using his modification of Ehrlich's methylene-blue method, observed in the ganglion cells of the retina large fibrils, which passed from one dendrite to another. Flemming (140) confirmed his previous observations upon the structure of the spinal ganglia and gave a further description of the fibrils of the nerve-cell protoplasm. He noted, also, the presence of a granular, faintly colourable, interfibrillar substance. Towards the close of 1895 Nissl (370), who had previously attributed to the unstained portion of the cytoplasm an unorganised or granular character, stated that he was now convinced after seeing Becker's preparations that it contained fibrils.

In 1896 Lugaro (239) maintained that there is a protoplasmic texture in the achromatic part of the protoplasm

and that the chromatic part passively occupies the interstices left by the achromatic texture; the achromatic part is constituted by the thread-mass of Flemming. In support of this view, he pointed out certain features of the disposition of the chromatic substance which suggest that it fills up spaces left by the fibrils. Moreover, in the part which appears homogeneous in preparations by Nissl's method, a fibrillar structure can be demonstrated by other methods. It has a fasciculated appearance in the processes, a reticular in the cell-body. A further argument in support of this view he drew from the existence of unipolar nerve-cells. In these elements there must be an independent and inverse conduction. The only solution of the difficulty as to how this can occur lies in the hypothesis of the existence of a fibrillar structure and of an isolated conductibility in the single fibrils of tracts apparently homogeneous. In a later paper (242) he described further observations upon the fibrils of the achromatic substance, made with the aid of staining with Delafield's hæmatoxylin and with the iron hæmatoxylin method, in the early stages of chromatolysis, when, owing to disappearance of the chromatic substance, the fibrils of the achromatic part are more easily discernible. Ramon y Cajal (426) expressed the opinion that the fundamental substance, not only of the nerve-cells, but also of the axis-cylinder, is formed of trabeculæ of achromatic substance in which the longitudinal trabeculæ are larger than the transverse, and that the fibrillar aspect seen by others is due to the retraction of the cytoplasm, on account of which there is seen only the longitudinal trabeculæ (Levi, 262). Levi (260), in his studies upon the fuchsinophile granules in the nerve-cells of the spinal ganglia, obtained with Galeotti's staining method a demonstration of fibrils exactly coinciding with those described by Flemming. Lenhossék (280) stated that he had found in the dendrites of the cells of the anterior horn of the spinal cord of the frog and in the cells of Purkinje of mammals three to seven striæ, which were continued into the fundamental substance of the chromophile particles and which simulated a fibrillar structure, but which he maintained could not be interpreted

as fibrils (Levi, 262). Flemming (141) described the fibrils of the achromatic substance in the cells of the cord of *gadus callarius*. He was able to satisfy himself that they form a reticulum in the cell-body. Sczawinska (486) found in the protoplasm of the nerve-cells of the anterior horn of the cord of the skate a fibrillar network, not only in the cell-body, but also in the protoplasmic and axis-cylinder processes. W. H. Cox (94) described the arrangement of the fibrils in the cells of the posterior root ganglia as observed in preparations by a new method of his own. The appearances suggested the presence of a network, but he seems to have been unable to determine its existence definitely. Dogiel (118) has distinguished two systems of fibrils in the cells of the spinal ganglia of mammals from results obtained with his vital methylene-blue method. One is peripheral and formed by fibrils which converge in the axis-cylinder process. The other is situated in the central part of the cell. Regarding the cell as a sphere, he looks upon the former as a system of parallels and the latter as a system of meridians.

In 1897 van Gehuchten (168) maintained that the achromatic substance consists of an organised and a non-organised part. The former has a reticular structure and represents the true cellular protoplasm. Lugaro (245), in the course of his studies upon the nerve-cells of the dog in poisoning by arsenic and lead, found that a very clear demonstration of the primitive fibrils could be obtained with Delafield's hæmatoxylin in cells which had undergone partial chromatolysis as the result of the action of the first of these poisons. He gives a minute description of the arrangement of the fibrils in the cells of the spinal ganglia, and formulates certain general conclusions regarding the nerve-cell of which the following are of interest here: The achromatic part of the nerve-cell contains the organs of nervous conduction, the fibrils, which in the protoplasmic prolongations run parallel, and in the body form networks which anastomose in various ways and constitute a true reticulum, the configuration of which varies with the various types of cell. The chromatic part is disposed passively in the interstices

left by the achromatic part, so that it gives us a rough negative image of the disposition and course of the bundles of fibrils which enter the cell-body from the prolongations. Levi (262) in his comparative researches upon nerve-cells paid special attention to the arrangement of the fibrils of the "fundamental part." He found that the cells of the spinal ganglia of *bufo* and *zamenis*, and the ventral cells of the cord of *scyllium*, are specially suitable for the study of these fibrils. The differences of arrangement presented in different animals he found to be considerable. He believes that the fibrils are not long and independent, but form anastomoses which are difficult to see, because hidden by the fibrils that interweave in every direction. These anastomoses are less numerous in those parts of the cell concerned more with conduction than with the performance of the specific function, and may be absent in parts exclusively conductive. The bundles of the fibrils in the dendrites go to clothe the superficial part of the cell-body, sometimes passing from one dendrite to another, sometimes turning down towards the deep part of the cell, where the fibrils crossing in every direction form a true network with large meshes. He finds that, as a rule, the axis-cylinder arises from the centre of the cell from an achromatic fibrillar cone which is never in relation with the parallel fibrils of the peripheral portion of the cell, and he therefore associates himself with the opinion of Lugaro (247) that the fibrils of the axis-cylinder originate from the reticulum in the deep part of the cytoplasm. The fibrils of the axis-cylinder are always parallel and only slightly undulated. He has been unable to demonstrate fibrils in the protoplasm of the karyochrome cells. He describes the vortices of the nerve-cells of *bufo* and compares his observations with those of Lenhossék upon the occurrence of a centrosome and sphere in the cells of the spinal ganglia of *rana* (Section I. 4). Ramon y Cajal (431) described the arrangement of the achromatic reticulum in the cells of the spinal cord. He drew attention to the occurrence of little chromatophile bodies at the nodal points of the reticulum of the cell-body, excepting at the origin of the prolongations. He could not exclude

the possibility that this reticulum is produced by coagulation of the protoplasm by fixatives, but thought there were many considerations strongly in favour of the view that it is preformed. Nissl (371) described the fibrils to be observed more especially in the cells of the anterior horn of the spinal cord of the calf in preparations by Becker's method. He expressly stated that it is possible to follow the continuity of numerous single fibrils through the whole cell-body. No difference could be observed in the appearance of the fibrils in the dendrites and neurites. Marinesco (313) described in the achromatic portion of the nerve-cell a ground substance and a substance which has a fibrillar structure in the processes and a reticular structure in the body of the cell. There is an anatomical continuity between this network and the fibres in the processes. In another paper (316) he stated that the formed achromatic substance (as seen in the cells of the spinal cord and spinal ganglia in peripheral chromatolysis) is constituted by a network which gives the cell a spongy appearance. The fibrils are attached to the periphery of the cell and to the wall of the nucleus. There are nodes at the points of intersection of the threads. The achromatic network (the spongioplasm) is the frame-work of the cellular edifice. Its disposition and texture regulates the form of the chromatophile elements. In the *Rapport* (314), which he presented to the International Congress of Moscow, he gives a detailed description of the achromatic fibrils, specially mentioning the occurrence of little chromatic swellings at the points of intersection of the threads, which he terms "nodal points." He defines the relationship between the fibrils of the nervous prolongation and those of the network of the cytoplasm. The parallel fibres of the axis-cylinder as they enter the cell break up into several bundles, of which one turns towards the centre, the others towards the periphery of the cell. They give off branches by which they establish an anatomical continuity with the network of the cytoplasm. Van Gehuchten (169), in his communication to the Congress of Moscow, described the achromatic network of the nerve-cell as forming not only the essential part of the cell-body, but also the regular con-

stituent part of the processes. In the protoplasmic processes the fibrils have a somewhat granular appearance, while in the axis-cylinder they are regular and distinct. Held (202) believes that the nerve-cell protoplasm and its prolongations have an alveolar or honeycomb structure, and maintains that the appearance of fibrils is artificial. Lenhossék (281) maintained his opinion that the achromatic part of the nerve-cells of the spinal ganglia of mammals has not a fibrillar character, but only a finely honeycomb structure. He admitted, however, the presence of fibrils in the axis-cylinder and in its cone of origin. Flemming (142), in a paper in which he criticised Lenhossék's views, maintained that the fundamental substance of all nerve-cells has a fibrillar structure. The fibrillation is longitudinal and radiated at the point of origin of the processes, reticulated in the rest of the cell-body. Pugnat (393) studied the spinal ganglia of reptiles and confirmed several of the observations previously made by Levi regarding the arrangement of the fibrils. Bethe (46) described in certain invertebrates and in the frog the complete or partial passage of the fibrils through the body of the nerve-cell from process to process without the formation of a network.

In this place the description of the primitive fibrils given by Apathy (8) would in ordinary course require some reference. But it will be more convenient to postpone consideration of the peculiar views advanced by this observer to another section (I. 9).

Writing in 1898, Cox (95) distinguishes in the cells of the spinal ganglia of the rabbit two kinds of fibrils, one long and straight, similar to those of the cone of origin of the axis-cylinder, and running in the achromatic intervals, the other short and tortuous and enclosed in the chromatic particles. He is inclined to believe that the fibrils are independent and that the appearance of a reticulum is a fallacious one (Lugaro, 253). Lenhossék (282) has now been able to obtain a satisfactory demonstration of a fibrillar structure in the nerve-cells of the frog and an indication of it in the peripheral stratum of the cells of the spinal ganglia of mammals. Auerbach (9) describes in the cells of the

spinal ganglia of the guinea-pig and rabbit a reticulum of fine fibrils with swellings at the nodal points. He has observed these nodal points in the cone of the axis-cylinder as in the rest of the cell, and believes, therefore, that it also is constituted by a fine reticulum. He states, however, that he is convinced that the structure is not truly reticular but alveolar, and that the appearance of fibrils is due to the action of fixatives. Ramon y Cajal (434) has observed in the cells of the spinal ganglia of the cat, with staining by Delafield's hæmatoxylin, an evident fibrillar structure of the axis-cylinder process continuous with a reticulo-fibrillar structure extending throughout the body of the cell (Lugaro, 253). Arnold (18), from results obtained with a special method of fixation, is persuaded that the achromatic substance has no definite fibrillar structure, although it contains some threads which appear to be continuous with the thread-net of the nucleus. Bühler (41) thinks that two kinds of fibrillar formations are to be distinguished in the nerve-cell protoplasm. Firstly, there are long fibrils continuous with those of the axis-cylinder and constituting the paths of conduction; secondly, there are short fibrils anastomosing in a reticulum which pervades all the cell, including the axis-cylinder, and which constitutes the fundamental substance of the cell, the neuroplasma (Lugaro, 253). Bethe (47-48) describes the pictures obtained by means of his new staining method for the primitive fibrils. The fibrils of the axis-cylinder are quite isolated from each other. The substance between them is homogeneous. In the body of the nerve-cells the fibrils likewise appear as well individualised, deeply-stained structures. In some cells it is possible to follow all the primitive fibrils continuously from process to process through the cell-body. In other cells their course cannot be made out. He rarely saw any evidence of division of the fibrils. There is no network of fibrils, but only a felt-work composed of isolated threads. He could not find any junction of them with each other. A large number of the fibrils of one dendrite pass into a neighbouring dendrite, in some instances without ever really entering the cell-body. He describes the course of the

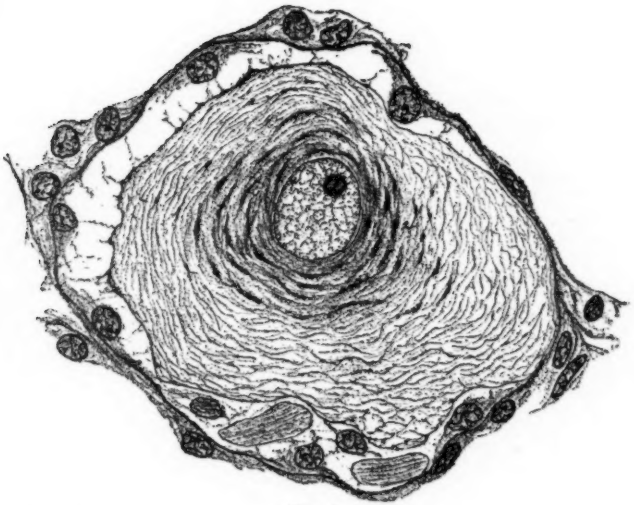

FIG. 3.

Cell of spinal ganglion of dog poisoned with arsenic, showing concentric arrangement of chromatic particles and fibrils. Section in the plane of the course of the fibrils. Owing to peripheral chromatolysis the fibrils are distinctly visible. Sublimate. Delafield's hæmatoxylin. (Lugaro 253.)

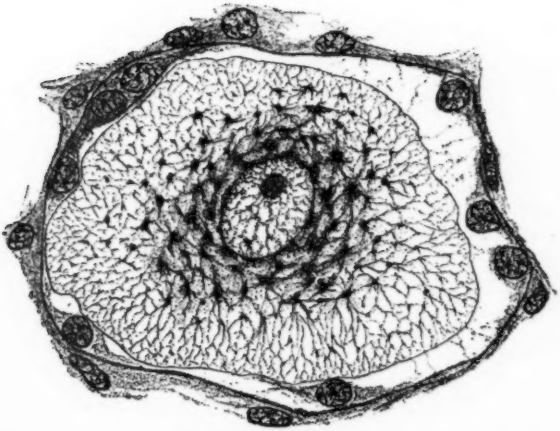

FIG. 4

Same as Fig. 3, except that the section is in a plane perpendicular to those in which the concentric fibrils run. (Lugaro 253.)

fibrils in the various forms of nerve-cell. Lenhossék (284) considers that confirmation of these observations of Bethe is required before they can be accepted as accurate. Marinesco (322), in describing the achromatic reticulum in the sympathetic ganglia, expresses the opinion that the nodal points are formed by true enlargements at the crossing of the fibrils, and therefore should not be thought to be of the same nature as the blocks of chromatic substance. Lugaro (250) directs attention to the beautiful demonstration of a reticulo-fibrillar structure that can be obtained by hæmatoxylin staining of nerve-cells, of which the chromatic part has been altered by experimental pyrexia, and gives a further description of the appearances presented by the primitive fibrils. The same authority (253), in his important paper upon the nerve-cells of the spinal ganglia of the dog, passes in review the previous observations upon the structure of the fundamental substance, and records results of further investigations of his own. He states that there can now be recognised as generally predominant the tendency to admit a reticulo-fibrillar structure, although with regard to certain points there is still considerable disagreement among the individual observers. He himself defends the reticulo-fibrillar theory against that of independent fibrils. He thinks that the various discordant opinions regarding the fibrillar structure are to be attributed largely to erroneous interpretations of the different aspects presented by different cellular types, and even by the same cell from different points of view. The aspect of the fundamental substance varies in different parts of the cell and also according to the direction in which the section of the cell is made. In one plane there may appear a structure of concentric fibrils and in a plane perpendicular to this a reticular structure. This fact has been already noted by Flemming (142). The greatest differences of aspect in the structure of the fundamental substance are, however, those due to difference of cellular type. He gives a minute description of the arrangement in each of the five different types of cell recognised by him in the spinal ganglia of the dog. He incidentally states that the chromatic thickenings at the nodal points do not

constitute an integral part of the reticulum, and that they have only a relation to the fibrils of simple super-position. It will be seen that upon this point his opinion differs from that of Marinesco. In all the types the fibrils of the axis-cylinder break up among the fibrils of the cytoplasm, joining with them and thus gradually losing themselves in the reticular formation. He thinks that the different types of penetration of the axis-cylinder described by Cox (95) are but different sectional aspects of the same mode of penetration. He also thinks that the conclusions of Bühler and of Cox regarding the existence of two kinds of fibrils are founded on false interpretations of the different aspects that the same cell can present in different parts and from different points of view. Levi (266), in the course of his study of the changes occurring in the nerve-cells of cold-blooded animals during hibernation, obtained some very clear pictures of the arrangement of the fibrils, which he describes in minute detail. A large part of this paper is taken up with a comparison of the author's observations upon the structure of the vortices with those of Bühler, a subject which will be dealt with in the next subsection. The observations of Donaggio (105) upon the cellular reticulum revealed by a special method will also be more conveniently considered in another subsection (I. 6). Ewing (135) admits the existence of a reticulum in the cell-body, but he regards it as a chromatic reticulum rather than an achromatic. "The strictly achromatic substance of the cell" he describes as granular both in the cell-body and in the axis-cylinder process. Gowers (182) has recently taught that the primitive fibrils pass through the body of the cell without interruption. He bases this contention chiefly upon the observations of Max Schultze.

The gemmulæ of the protoplasmic processes.—As these structures form a part of the achromatic substance of the nerve-cell, they require notice in this place. The recent observations which specially relate to them are not numerous. The most important are undoubtedly those of Hill (204-205) and Lugaro (252). Hill notes the fact that S. Meyer (345) could not find them in preparations by Ehrlich's

methylene blue method, and therefore questioned their existence as real structures; and that, on the other hand, Ramon y Cajal (425) observed them by this method both in the young animal and in the adult. The view of Kölliker (229) that they only occur in the adult as artefacts is now quite untenable. Ramon y Cajal (425) made use of a modification of the methylene blue method for their demonstration, and expressly states that the Erlich-Dogiel process does not reveal them, but shows varicosities upon the protoplasmic processes which he regards as a *post-mortem* product due to the action of the air. In a later paper (429) he gives a further description of the gemmulæ as seen in his methylene blue preparations, and states the conclusion that they serve to increase the surface of connection of the protoplasmic arborisation. Hill thinks that the thorns are organic structures which are not shown in their entirety by the chrome silver method, and that the typical form of a rod with a dot at the end is due to a *post-mortem* change in the tissue. He describes the numerous variations in form which they present. He believes that they are really the ends of unstainable nerve filaments surrounded by a film of staining cell-plasm. He has observed that in the cells of Purkinje in the skate they are replaced by long striæ streaming away from the protoplasmic process on either side. Lugaro (252) has demonstrated the functional mobility of the gemmulæ, their general expansion during sleep, and their contraction under the influence of certain stimuli. The results of his observations, and the technique employed, exclude the possibility that their typical appearance is one artificially produced by *post-mortem* change.

(4) *Centrosome and Sphere of Lenhossék.*—*Vortices of Levi.*

In 1895 Lenhossék (278) described in the cells of the spinal ganglia of the frog a figure to which he applied the term *centrosome and sphere*, and which he demonstrated especially in iron hæmatoxylin preparations. He found that in certain cells the nucleus is eccentric, and that on the

side to which the greater part of the protoplasm is placed there is a concentric arrangement of the protoplasm. The central point of this figure, the *centrosome*, is somewhat granular, and surrounding it there is the more homogeneous *sphere*. It is to be borne in mind that at this period Lenhossék denied the existence of fibrils in the body of the nerve-cell. Dehler (106) shortly afterwards confirmed Lenhossék's observation, and similar figures were described by Bühler (40) in *lucertola*, by J. Schaffer (470) in *petromyzon*, and by Lewis (271) and Maclure (354) in the nerve-cells of invertebrates.

In 1897 Levi (262), in the course of his comparative researches, observed in the protoplasm of the cells of the spinal ganglia of the toad the occurrence of a spiral vortex composed of converging fibrils, and having a distant resemblance to the centrosome and sphere described by Lenhossék in the frog. He observed similar figures in the frog and in *zamenis*, but they were less distinct. He states that he is satisfied that what Lenhossék regarded as a homogeneous sphere is really composed of a vortex of fibrils, and that his centrosome is a transverse section of the axis of this vortex. He therefore maintains that one cannot give to this figure the significance either of a centrosome or a sphere, more especially since he has been able to trace the fibrils of the vortex into direct relationship with the origin of the axis-cylinder. This consists badly with the meaning that is commonly given to the term *centrosome*, *i.e.*, a formation which, at least at a certain period of ontogenetic development, takes an active part in the reproduction of the cell. In his paper upon karyokinesis in the nerve-cell, Levi (264) maintained the same view regarding the nature of this so-called centrosome and sphere. He could see no reason for doubting that the centrosome of the somato chrome cells, like that of the *kernzellen* (in the case of which he has proved the point) resides in the nucleolus. Bühler (41) in his work on the nerve-cell, devotes a chapter to the subject of the concentric figure described by Lenhossék, and entirely confirms Levi's statements regarding it. He also gives a description of another structure which he was the first to

observe in the nerve-cell (40), namely, the "centrirte system" of Heidenhain. "It is a system of organic rays with central corpuscles and microsomes." It is placed between the nucleus and the inferior pole of the cell, but resides in the proximity of the inferior margin of the nucleus. Often it is double, and always lies on the principal axis of the cell, or in immediate proximity to it. Its presence in the cells of the toad and frog is constant (267). Szczawinska (487) has recognised in the nerve-cells of the skate figures similar to those described by Levi and Bühler. Levi (266), in his recent paper upon the changes in nerve-cells during hiber-

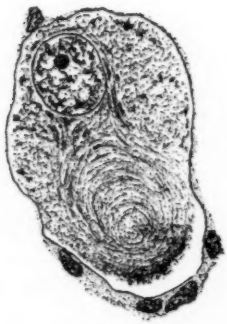

FIG. 5.

Cell of spinal ganglion of *Bufo vulgaris*. Winter. Shows the spiral vortex in oblique section. (Giuseppe Levi 266.)

nation, gives a very minute description of the vortices as they occur in the toad, and compares his description with that of Bühler, which differs in certain points of detail, more especially as regards the relations of the "rectilinear fascia" and terminal spiral of the vortex to the axis-cylinder process. He now recognises that it is only during hibernation that a clear view of these formations can be obtained, as at other times they are obscured by the chromophile elements. His description of the fibrils of the vortex and their relation to the axis-cylinder and nucleus is of much interest, but scarcely admits of being epitomised.

(5) *Physiological Pigment.*

No very important light has recently been thrown upon the question of the nature of the physiological pigment of the nerve-cell. The only paper that has appeared on the subject during the period under review seems to be that of Pilcz, although there have been numerous incidental references to it. Schäfer (471) maintained that the presence of pigment is not a sign of decadence, but rather one of activity. Pilcz (392) has distinguished two kinds of nerve-cell pigment, which are different as regards their development, and react differently to staining reagents. One is pale yellow, and occurs in the cells of the cerebral cortex, basal ganglia, cord and spinal and sympathetic ganglia. The other is dark brown, and is present in the cells of the locus cœruleus, substantia nigra of Sœmmering and nucleus of the vagus. These two kinds of pigment are not different forms of the same substance, but of an entirely different nature. The yellow pigment is blackened by osmic acid, the brown is not. Neither of them are hæmatogenous. He has studied the period at which these pigments make their appearance in development. The brown pigment first appears in the cells of the locus cœruleus at the twelfth month. In general it appears at an early period of life, and ceases to increase after a few years. On the other hand, the yellow pigment is first seen (in the spinal ganglia) about the sixth year, and continues to increase throughout life. In the lower animals this pigment is much less abundant than in man. It is never found in the cells of Purkinje. Hutchison (209) found that an amount of pigment, far in excess of the ideal standard, was present in nearly 50 per cent. of presumably healthy human brains. Rosin (447) found that the yellow pigment in the nerve-cells of the human cord is blackened by osmic acid, but that this reaction does not occur if the preparations are first treated with ether. He therefore thinks that it is partly of a fatty nature. Colucci (89) states that chemical reactions prove that the yellow globules in nerve-cells are not fat. They may, however, undergo a fatty metamorphosis and then a black reaction is obtained with

osmic acid. He regards them as a manifestation of cellular metabolism. It has not been proved that they are true pigment granules such as those in the cells of the locus niger, &c. Marinesco (318) believes that the yellow substance in the nerve-cells arises from a transformation of the chromatophile particles, and that it is allied to fat. He notes that it stains with basic fuchsine, with hæmatoxylin in Weigert's method, and with osmic acid. Lord (289*a*) holds that the pigment of the nerve-cell results from fatty degeneration of the "ovoid bodies" (chromophile elements).

(6) *Golgi's Pericellular Reticulum.*

In April and July of last year Golgi (159-160) made two communications, in which he described two new structural features which he has observed in the nerve-cells in preparations by his rapid silver method, or by special modifications of it. The first consists of a peculiar reticular investment of the cell, the second of an entirely separate reticulum within the cell-body. On account of the great interest of the subject, I think it is well to give a somewhat detailed account of these observations here. I am indebted to Professor Golgi for very kindly sending me reprints of his papers.

The pericellular investment (159) is a very delicate structure formed of a substance clearly differentiated from the cell-body. It sometimes appears as a reticulum, sometimes as a continuous homogeneous stratum, or as closely applied squames. Not rarely it presents striations which might be interpreted as fibres crossing over the cell-body. Most frequently it has a finely reticulated structure, with round, uniform, regular meshes. It forms a cuirass which clothes not only the cellular body but also the protoplasmic prolongations, along which it may be followed even to the subdivisions of the second and third order. Upon these, however, it loses its reticular aspect and becomes a uniform stratum. The cellular substance, including the prolongations, remains colourless and transparent. The investment is seen in its most characteristic form upon the cells of the spinal

cord, nuclei of the medulla, dentate nucleus of the cerebellum, &c., but it may be seen upon all varieties of nerve-cell, even the smallest. The cells of Purkinje show it generally as a continuous investment or composed of fine little squames. In the cells of the cerebral convolutions it is commonly uniform and continuous, although the reticular form may also be observed in some. Golgi states that in 1882 he expressed the opinion that it is probable that the nerve-cells possess an investment of the nature of neuro-keratin. In 1893 he spoke more decidedly regarding the existence of such an investment, and invoked it as an argument against the theory of transmission of the nervous current by contiguity (156). In 1895 Lugaro (237) described a similar appearance of the cells of the dentate nucleus of the cerebellum, stating that in silver preparations these cells appear as if invested by a brown shell, which is homogeneous and riddled with holes. Golgi refers also to a somewhat recent paper by Martinotti (299), in which there is described a similar reticular investment of the nerve-cells of the spinal cord which the author thinks may be composed of neuro-keratin. Shortly after Golgi made his first communication, Lugaro (251) published a reply to it on account of certain references which it contained to his observations and views. He points out that he did not give to the structure in question the value of an integral part of the nerve-cell (as Golgi seems to do), but only that of an interstitial substance. More recent observations have still more fully convinced him of the correctness of this view. He finds that the aspect of a cellular investment is only obtained when the cells are at a certain distance from each other. Where they are crowded together the apparent investments tend to become confluent, so that there results that picture which Cajal described, and compared to the aspect of a honeycomb. He cannot affirm with certainty what is the nature of the part that colours, but is inclined to regard it as an interstitial liquid.

The reticular figure described by Donaggio (102-104) has certain points of resemblance to Golgi's pericellular investment, but, as he has lately (105) identified it with the achro-

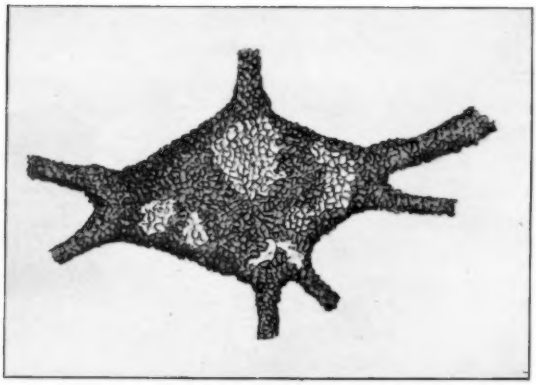

FIG. 6.

Nerve-cell with reticular investment. Cell of anterior horn of spinal cord of cat. (Golgi 153.)

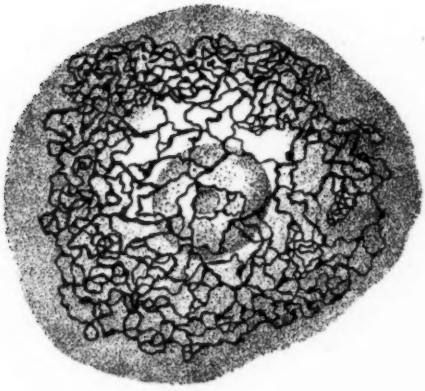

FIG. 7.

Spinal nerve-cell with internal reticular apparatus. From a ganglion of adult dog. (Golgi 160.)

matic reticulum, and as it has to be compared also with Golgi's internal reticulum, I defer consideration of it to the next subsection.

(7) *Golgi's Endocellular Reticulum.*

Golgi (159), in the first of his two recent papers just referred to, describes this structure as a delicate and beautiful reticulum hidden within the cell-body. It has a characteristic aspect on account of which, if the reaction happens to be partial, even little fragments of it can be recognised. It is best examined in mounting media of a lower refractive index than Canada balsam, such as glycerine. It consists of threads of irregular thickness, often somewhat tortuous, which freely anastomose with each other. Between its peripheral limits and the surface of the cell there remains a zone of clear cell-protoplasm. While externally the reticulum is sharply limited, towards its inner aspect, around the nucleus, the threads dip down to different levels. Some of those derived from the peripheral plane present short offshoots which terminate as delicate pyriform swellings. Similar swellings may occur in the course of the threads, more especially at the nodal points. The reticular body has in relation to the whole cell a definite orientation, which, however, presents certain differences in the various categories of cells. In the cells of Purkinje (in which alone up to this time he had made an extensive study of it) the reticulum tends to assume the form of a pear, with the narrow end directed towards the molecular stratum, in correspondence with the point of exit of the large protoplasmic prolongation, in which the various threads run together into one, two or three terminal threads.

In his second paper (160) he states that he believes that this internal reticulum occurs in all the principal categories of nerve-cells and gives a minute description of it as it appears in those of the spinal ganglia of the dog. Its characters here are very similar to those already described in the cells of Purkinje, but, at the same time, they present characteristic differences. It has a globose form, adapting

itself (as in other situations) to that of the cell, and it has no special orientation. The reticular constitution is less distinct, giving place to what is rather an irregular filamentous apparatus, complexly convoluted, the threads of which it is difficult to trace. There is undoubtedly, however, the structure of a network. With advancing age, the reticular

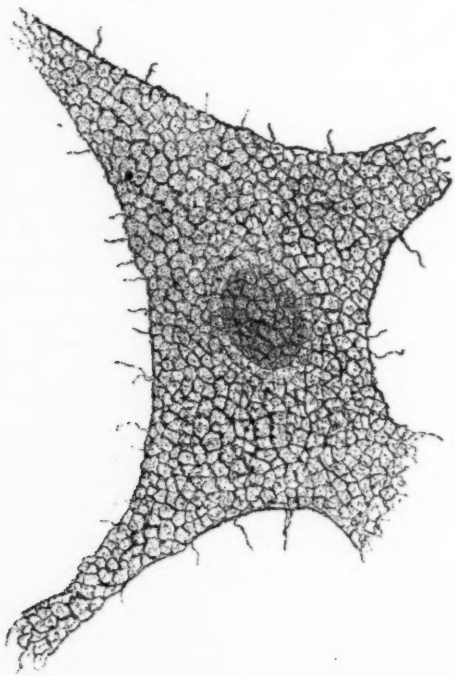

FIG. 8.

Nerve-cell of anterior horn of spinal cord of dog, showing reticulum. The original is in colour. Donaggio's methylene blue method. (Donaggio 105.)

character seems to become more pronounced. Some of the threads are very fine and of regular thickness, others in the same cell may present a succession of dilatations and constrictions. They may give off some lateral processes which may terminate after a short course in rounded or oval

swellings. There is generally a clear zone around the nucleus, but occasional threads appear to terminate in contact with it. He believes that this reticulum is something absolutely different from the Nissl-bodies and primitive fibrils described by others.

Donaggio (102) in 1896, by means of a modification of the vital methylene-blue method, obtained in the nerve-cells of various mammals a demonstration of a fine reticulum, extending throughout the cell-body and protoplasmic prolongations and connected on the one hand with the nuclear network and on the other with fibrils outside the cell. Two years later (104) he described this reticulum more minutely, but came to no very definite conclusion regarding its significance. Quite recently he has published a third paper on the subject (105). He now considers that the reticular figure corresponds to that of the achromatic reticulum of the protoplasm. He has observed, however, that it is most brightly coloured in those parts in which the chromatic substance is known to be most abundant, that is to say, in the cell-body and initial portion of the protoplasmic prolongations, while in the branches of the protoplasmic prolongations it is not visible, and in the cone of the axis-cylinder it is constituted by only very faintly-coloured threads. Further, the deeply-coloured threads present a granular surface, and some cells show an initial formation of chromatic particles. He therefore concludes that the network is formed of threads which consist of two substances, one which is deeply coloured with methylene-blue and corresponds to the chromatic substance shown by Nissl's method, and one which is colourless in preparations by that method. He differs from the opinion of Held, according to which the chromatic substance is dissolved in the protoplasm, and maintains that its normal disposition is on the threads of the achromatic reticulum and that it is for this reason that his method, which does not alter this original disposition, reveals the reticulum. He thinks that up to a certain point a comparison is possible between this reticulum and the two described by Golgi. He cannot, however, by his method see any difference between the

external portion and that in the deeper part of the cell. There appears to be only one continuous structure.

Superficial reticular formations analagous to that described by Donaggio have been described by Nissl (374) and Bethe in preparations by the method of the latter. These authorities maintain that these reticula do not belong to the nerve-cell but to the interstitial nervous network which they believe to occur throughout the grey substance (257). Ramon y Cajal (435) opposes this view, and maintains that the pericellular reticulum is merely the more superficial and coarser part of the spongioplasm to which the colouration is sometimes limited in preparations by Erhlich's method. It belongs to the cell and has no connection with the nervous filaments that surround it. He regards the figures described by Golgi as produced by colouration of the interstitial cement, of the superficial network, or, in certain instances, of pericellular nests. In any case, there is no reason to consider the superficial network as either an isolating investment or as a pericellular plexus (257).

(8) *Nucleus and Nucleolus.*

Of the many important contributions that Giuseppe Levi has made to our knowledge of the normal anatomy of the nerve-cell, there is probably none more valuable than the clear and precise description that he has given of the structure of the nucleus. Previous to his taking the matter up, the study of this portion of the nerve-cell had been comparatively neglected, and all descriptions that had been given of it were more or less inaccurate and incomplete. The publication of his first paper on the subject in 1896 may justly be said to mark one of the important epochs in the history of the progress of our knowledge of nerve-cell anatomy.

Flemming (139), in his early paper upon the cells of the spinal ganglia, expressed the belief that both the nuclear membrane and nucleolus are rich in chromatin. Nissl (360) in 1893 described a nuclear membrane, a reticular framework, from one to three nucleoli and also acces-

sory nucleoli. In the same year, Rosin (446), basing his conclusions upon results obtained with Biondi's stain, maintained that the nucleus and nucleolus are neutrophile. In 1894 Nissl (361) differentiated in the nucleolus a delicate external layer, which stained deeply, and a central colourless part. In 1895 Lenhossék (277) described a very delicate nuclear membrane and a faintly-staining nuclear reticulum. In the nucleolus he distinguished a group of from three to five punctiform, strongly colourable endonucleoli. Dehler (106) noted at the periphery of the nucleolus a deeply-staining zone. Roncoroni (443) described in the nuclei of some of the pyramidal cells of the cerebral cortex the occurrence of a sharp line, coloured deep blue in methylene-blue and eosine preparations, and extending sometimes from one pole of the nucleus to the other. He thought that it was probably composed of chromatin. Lugaro (240) maintained that Roncoroni's line is nothing more than a fold of the nuclear membrane, due to shrinking of the nucleus, generally from alcohol hardening, and that staining reactions prove that it is not composed of chromatin. Roncoroni (444) defended his original opinion against the criticisms of Lugaro, who, in turn, replied with further arguments in support of his contentions (241). There can be little doubt that Lugaro's view of this matter is the correct one.

In 1896, Ramon y Cajal (426), from studies with the method of Nissl, concluded that the nucleus of the nerve-cell undergoes, along with its differentiation, a process of simplification consisting in a progressive concentration of all the nuclein in one or two spherical nucleoli, and that it is probable that nerve-cells with the nuclein thus concentrated have lost the power of proliferation. He believed that in the large cells the nuclear contents were devoid of nuclein, but that, on the other hand, the nucleolus was formed entirely of nuclein, which, however, was modified in the central portion by long mitotic repose. Levi (259) published his first paper upon this subject contemporaneously with the preceding. He pointed out that Rosin's conclusion that the nucleus and nucleolus of the nerve-cell are neutrophile is in contradiction to established views regarding the

structure of nuclei in general, since it is now believed that the chromatin (or nuclein) of the nucleus has affinities for the basic aniline dyes, the nucleolus for the acid. He considers that Rosin used Biondi's stain in too concentrated solution, and therefore obtained reactions which were largely artificial. It is now known that for elective colouration dilute solutions which stain slowly and progressively are always to be preferred. He has himself employed this progressive method of colouration with Biondi's stain (after sublimate fixation) and has obtained results entirely different from those of Rosin. He finds that in the somatochrome cells all the different elements—including the Nissl-bodies and the achromatic part of the protoplasm, the nuclear membrane and nuclear granules or network—take the acid stain (acid fuchsine and orange G), excepting from

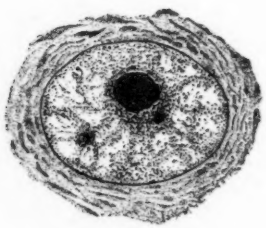

FIG. 9.

Nucleus of nerve-cell of anterior horn of spinal cord of guinea-pig, showing basophile particles attached to the nucleolus. The original is in colour. Ehrlich-Biondi staining. (Giuseppe Levi 262.)

two to four particles adherent to the nucleolus, which take the basic stain (methyl green). The large globular nucleolus (or nucleoli, as there are occasionally two), apart from these particles, is very strongly acidophile. The basophile particles vary considerably in form and volume. They may have the aspect of semilunar bands or of spherical masses, or may assume any intermediate form. He has never seen them detached from the nucleolus, nor has he seen other basophile particles among the contents of the nucleus. He describes the special features of the basophile particles in the somatochrome cells of different regions. In the anterior

horn of the spinal cord, for example, they are constantly semilunar, delicate and elongated, so that often they embrace the voluminous nucleolus in a green ring. He also describes the somewhat different characters presented by the nuclei of the two varieties of karyochrome nerve-cells, but this subject is more fully dealt with in a later paper (262-263). He has never seen in his preparations the endo-nucleoli to which Lenhossék refers. The accessory nucleoli that have been described evidently correspond to the acidophile granules, some of which, at least, in lower vertebrates, are little inferior in volume to the nucleolus. They differ, however, from the latter in never being surrounded by basophile particles. He maintains that the basophile particles are composed of nuclein (chromatin) and that they constitute the whole of this substance contained in the somatochrome nerve-cells. In the course of his observations upon the fuchsinophile granules of the nerve-cell, he observed (260) that the basophile particles of the nucleoli of the cells of the spinal ganglia are rounded in form in the resting condition and elongated in that of fatigue. This change he attributes to the enlargement of the nucleolus, which occurs in the latter condition, according to the observations of Mann and Lugaro. In his comparative researches upon nerve-cells, of which he published his account in 1897, Levi (262-263) included the study of the characters of the nuclei. He confirms his previous description, more particularly as regards what he terms the "centralisation of the nuclein in the somatochrome cells." He finds that the nuclei of this class of nerve-cells have essentially the same structural features in all the animals he has studied, but describes the various slight differences he has observed. He regards the nuclear membrane as a true membrane and not merely a part of the nuclear stroma, as in neuroglia cells. In mammals the nuclear reticulum, or lining network, is very loose and faintly colourable. While the centralisation of the nuclein is complete in the somatochrome cells of mammals, in all the lower vertebrates, although the greater part of the nuclein is centralised, there is a certain quantity of it diffused throughout the nucleus. The nuclei of the

kernzellen have a delicate, acidophile membrane. Their nucleoli present many variations. They are very small, generally irregular in outline and always composed of two substances, nuclein and one or two acidophile particles. Centralisation of the nuclein is, as a rule, only partial. In the granules of the cerebellum, &c., it is doubtful if the nuclear membrane is always acidophile. Acidophile substance is always present in the nucleus, but it is very scanty. Chromatin is, on the other hand, abundant. The nuclei of the neuroglia cells have a membrane composed of chromatin and a dense reticulum of the same substance. There is, however, no precise differential criterion by which it is possible to distinguish them from those of the granules.

Van Gehuchten (169) refers to Levi's observations, and gives a description of the nucleus essentially in agreement with his view, except as regards the nucleolus, which he seems to regard as composed entirely of chromatin. Lenhossék (281) confirms Levi's statement that the nuclear reticulum is always acidophile. He doubts, however, if the basophile particles in the nucleolus are a constant morphological feature, and thinks that their basophile character is only relative. As will be seen, he altered this opinion shortly afterwards. Prenant (400) describes the occurrence of crystalloid rods in the nuclei of the nerve-cells of the sympathetic ganglia of the hedgehog. They are straight or curved, generally long and intensely coloured.

In 1898 Bühler (41) distinguished in the nucleus of the nerve-cell an acidophile chromatin and a basophile; the first (oxychromatin) is much more abundant than the second. The nucleolus is composed of a substance very nearly allied to basi-chromatin but not identical with it. He did not refer to the special disposition of the nuclein described by Levi. Heimann (210) states that the nucleolus presents a resistance to stains similar to that exhibited by bacterial spores. He regards the nuclear reticulum as basophile (211). Lenhossék (282) considers that the terms acidophile and basophile should not be used in too absolute a sense with regard to the staining reactions of the constituents of the nucleus and nucleolus. He regards it as settled that the

nuclear reticulum of nerve-cells has only a very faint affinity for basic dyes, and that on the other hand it colours intensely with acid dyes. With regard to the nucleolus he now accepts the views of Levi.

It should be mentioned here that Goldscheider and Flatau (167), in a work which has probably been widely read in this country, gave an erroneous account of Levi's conclusions regarding the structure of the nucleus of the nerve-cell. Ewing (135) has also fallen into an error in his reference to Levi's description of the changes that occur in the basophile particles of the nucleoli of the cells of the spinal ganglia after prolonged stimulation of the sciatic, attributing to him the belief "that during cellular activity there is an increase in the size and number of the granules of true chromatin lying about the nucleoli of these cells."

Timofeew (506) states that the nuclei of the nerve-cells of birds have two nucleoli, one of which has the characters described by Levi, while the other is entirely acidophile.

In his latest paper on the subject of the nucleus, Levi (265) reviews the recent observations recorded by other authorities, and defends his opinions against certain criticisms that have been offered. He refers to the fact that his statement that the nuclear membrane of the large nerve-cells is always acidophile in reaction has been confirmed by Lenhossék (282), Ramon y Cajal (426) and van Gehuchten (169). He especially criticises the conclusions of Bühler (41), which differ essentially from his own. He maintains his statement that the basophile character of the nucleolar particles is absolute, and disputes the opinion of Ramon y Cajal (426) that the whole of the nucleolus is composed of chromatin, insisting on the acidophile character of the central portion.

(9) *Mode of Connection of Nerve-Cells.*

According to the neuron theory, every nerve-cell with its protoplasmic processes, axis-cylinder process and collaterals, is an anatomical unit, structurally independent of other nerve-cells; the nerve wave passes from one cell to another by

way of contiguous terminal arborisations of axis-cylinder processes and protoplasmic processes or nerve-cell bodies, never by anastomosing branches ; neither the network of Gerlach, formed by anastomoses of protoplasmic processes of adjacent cells, nor the diffuse network of Golgi, formed by the branches of adjacent axis-cylinder processes, have any real existence. The neuron theory has, however, always had its opponents, and at the present moment a most serious attempt is being made to entirely overthrow it. The evidence that had been adduced against it up to 1894 has been very clearly stated by Tanzi (499), and van Gehuchten (168), in the last edition of his text-book, gives an excellent historical account of the whole matter up till 1896. I shall notice here only some of the more recent observations that have been recorded in support of the existence of direct connections. In 1893 Dogiel (115) described in the retina various forms of anastomoses between nerve-cells. An excellent *résumé* of his views, as well as of those of others who have recently studied the cells of the same organ, will be found in van Gehuchten's book. Ramon y Cajal (428) and many other authorities deny the existence of anastomoses in the retina, while some observers (Renaut, 451, Bouin, 64, &c.) describe anastomoses of a different kind from those of Dogiel. In 1895 Golgi (158), in a paper upon the foot of the hippocampus, defended his views regarding the existence of a diffuse nervous network. In the same year Vassale and Donaggio (515) stated that in the cerebral cortex they had observed by means of a new chrome silver method appearances pointing to the existence of anastomoses between the gemmulae of the protoplasmic processes of nerve-cells and the fine ramifications of the axis-cylinder processes of other cells.

In 1896 Hill (204) from observations by the chrome silver method was led to regard it as at least possible that the thorns of the protoplasmic processes of the cells of Purkinje may contain the ends of the axis-cylinder processes of the granules.

In 1897 Held (202) stated that he had observed in the adult a true concrescence, a relation of continuity and not

simply one of contiguity, between the terminations of a branch of an axis-cylinder process, on the one hand, and the cell-body or protoplasmic process of another cell, on the other. He did not, however, consider that the existence of this relation disproves the doctrine of the neuron. In a later paper (203) he maintained that nerve-cells have two modes of direct union; firstly, that just referred to, and secondly by the branches of their axis-cylinder processes which terminate in a common pericellular network around another cell. In this year (1897) Apáthy (8) published an account of his remarkable observations upon the structure of the nervous system which constitute by far the most weighty evidence that has yet been advanced against the neuron theory. I have not had access to Apáthy's monograph, and know of his views chiefly through the very full *recensione* that has been given of it by Levi (268), and the critical paper of Barker (62). The following is a translation of Levi's review in so far as it relates to the subject of this subsection: "In this work of more than two hundred pages, with nine plates, the author describes the results of more than ten years of research, results which until now he has communicated only very summarily in short notes. The author promises to follow this paper with another, in which will be discussed the observations of preceding authors. He made his observations upon the central and peripheral nervous system of leeches and earthworms, and of certain vertebrates. The methods of technique adopted were the following:— Vital colouration by methylene blue; colouration in mass (of pieces fixed in sublimate) with hæmatein Ia; chloride of gold, making it act either upon fresh pieces, or upon pieces fixed in sublimate, or in other ways. The fundamental idea upon which the whole work is based is this: The nervous system is constituted by two kinds of very different cellular elements, nerve-cells and ganglion cells. The first differentiate in ontogenetic development into conducting substance, into primitive fibrils; the second become adult ganglion cells, and are united by the fibrils. The paths which in the adult are traversed by the fibrils are already traced out at an early period of development, and are repre-

sented by intercellular bridges. None of his methods, however, permit of the establishment of the precise moment at which the conducting substance is formed. The anatomical unit, truly specific of the conducting substance, is thus the primitive fibril, or neuro-fibril, which pursues uninterruptedly a very long course from the sensory cell, from which it originates, to the ganglion-cell, which it traverses, and from there it passes to a second and to a third ganglion cell, and then enters a muscular fibre. The neuro-fibril (*primitivfibrille*) is constituted by *elementarfibrillen* which are recognisable only when the fibril branches either in a ganglion-cell or in a termination; when this occurs it breaks up into its elementary constituents which, however, can unite again and form the continuation of the neuro-fibril. Between the neuro-fibrils there are very numerous anastomoses, represented, however, at least in the nerve-centres, by very delicate fibrils, which are destroyed in Golgi's preparations. Thus it is to be explained why hitherto the existence of such anastomoses has been denied. But not only between the peripheral fibres but also between the ganglion-cells there are anastomoses (cellular bridges). Another mode of union occurs by two ganglion-cells sending their axis-cylinder processes into the same nerve-fibre. The author, it will be seen, believes that he has demonstrated with facts what Gerlach advanced only as a hypothesis. He maintains that his fundamental law of the continuity of neuro-fibrils can be demonstrated also in vertebrate animals."

Levi appends to his *recensione* some words of criticism both of these views and of the description given of the internal structure of the ganglion-cells. He thinks that Apáthy's observations on these subjects do not differ much from those made recently on the structure of the nerve-cell of the vertebrates. The great difference consists in the inductions. The impression is aroused by the whole work that the author has wished to make these inductions uniform with a scheme. Certainly his observations often do not justify them.

The bearing of Apáthy's observations upon the neuron theory is dealt with in another section (IV. 1).

Blanes (52) concludes against the opinion of Golgi and Monti that a nervous reticulum formed by the collaterals of certain cells can be demonstrated in the olfactory bulb.

The numerous observations that have been made of the occurrence of twin cells and cells with lobes united to a central portion by means of fibrillar bridges, need scarcely detain us here (see Rossi (437), Pugnat (393), Levi (262), Marinesco (322), van Gehuchten (168)). In some instances they are to be explained as arrests of development, in others they appear to represent an exceptional but still normal condition in the adult, but in no case does their existence really affect the neuron theory. Capobianco and Fragnito (87) have recently maintained that direct connection of nerve-cells by their protoplasmic prolongations is a common histological feature, although one that does not readily admit of demonstration. They think that it cannot be explained as an error of development.

Semi Meyer (346) has observed a new mode of connection of neurons in the nucleus of the sixth nerve, consisting in the termination of certain axis-cylinders in spherical or elongated swellings which rest upon the bodies of the nerve-cells. L. Auerbach (10-11) has recently, with the aid of a new staining method, observed that the nerve-fibres which terminate around a nerve-cell are not independent of each other, but form a close network running parallel to the cellular surface. From this network short fibrils are given off which terminate upon the cell by little thickenings. They do not, however, establish any true continuity with the fibrils of the cell.

(10) *Morphological Classification of Nerve-cells.*

In 1894 Nissl (363) maintained that the various arrangements presented by the chromatic substance in the protoplasm of the nerve-cells of the central nervous system permits of the distinction of different types of cell. In the following year (365) he developed this idea further, and gave an elaborate classification of nerve-cells according to their morphology. He divided them into :—

(*a*) Cytochrome nerve-cells, or granules.
(*b*) Karyochrome nerve-cells, or nuclear cells.
(*c*) Somatochrome nerve-cells, or cell-body cells.

The cytochrome nerve-cells are small elements which present only a nucleus, the protoplasm being indistinguishable (in preparations by Nissl's method). The nerve-cells of the granular layer of the cerebellum are an example of this class.

The karyochrome nerve-cells differ from the preceding only in the larger size of their nucleus. Examples are seen in the cells of the *substantia gelatinosa* of Rolando.

The somatochrome nerve-cells have a cell-body which completely surrounds the nucleus, has a distinct outline and contains a stainable substance.

Virtually there are only two classes—the somatochrome and the karyochrome—the cytochrome cells being merely a variety of the latter.

Nissl divides the somatochrome cells into four groups, each of which again he divides into various types. The four groups are as follows :—

(1) *Arkyochrome nerve-cells.*—The colourable constituent is arranged in the form of a net-work.

(2) *Stichochrome nerve-cells.*—The colourable constituent is arranged in the form of parallel bands (motor cells, etc.).

(3) *Arkyostichochrome nerve-cells.*—The arrangement of a net-work and of parallel bands is combined. (Cells of Purkinje, etc.)

(4) *Gryochrome nerve-cells.*—The colourable constituent consists of small granules.

It is scarcely necessary to enter into the further details of this classification here. It has been much criticised, and little of it except its broad distinction of somatochrome and karyochrome nerve-cells is now in general use.

Van Gehuchten (168) thinks that the distinction between karyochrome and cytochrome cells is not justified, and that the division of somatochrome cells into different groups according to the special disposition of the chromatic substance has as yet only an exceedingly limited value. Colucci (88) thinks that the view of the nerve-cells obtained

by Nissl's method is too one-sided to allow of a classification being based upon it. Levi (262) thinks that nerve-cells have as yet been too little studied to permit of a morphological classification of them. In his description of the results of his comparative researches he retains the classification of Nissl merely for convenience, stating at the same time that the criteria of his distinctions are different from those of Nissl. Marinesco (314) has justly remarked that a rational classification of nerve-cells ought not to neglect either of the two organized elements of the cytoplasm. A classification having for its basis the chromophile elements alone is incomplete. *Goldscheider and Flatau* (167), on the other hand, think that Nissl's classification is not yet sufficiently valued.

(11) *Structural Changes accompanying Modifications of Functional State.*

I shall deal here only with observations upon structural changes in the strict sense, leaving the subject of alterations in the form of the nerve-cell (amœboidism or plasticity) to be considered in a later section.

The observations of Hodge in this field, as well as those of the next two writers mentioned, do not fall within the period under review, but as they require to be compared with later work I notice them briefly here.

In 1889 Hodge (196) described the changes produced in the sympathetic ganglia of frogs and cats by electrical stimulation of a nerve going to one or more of these ganglia. He found in the nucleus decrease in size, irregularity of outline, loss of open reticular appearance, darker staining; in the protoplasm, slight shrinkage, diminution of power to stain or to reduce osmic acid, vacuolation; in the cell-capsule, decrease in the size of the nuclei. In 1892 he described the following changes as produced in the spinal ganglia and brain of birds by fatigue (197) :—Diminution in size of nucleus, irregularity and jaggedness of its outline, darker staining of its reticulum, shrinkage of the cell-protoplasm, vacuolation (spinal ganglia), and enlargement of pericellular spaces. In 1892 Vas (510) found that stimula-

tion of the cervical sympathetic of the rabbit for fifteen minutes at a definite distance from the superior cervical ganglion, produced the following changes in the nerve-cells of this ganglion :—Increase in size of cell-body and nucleus, loss of chromatic substance around the nucleus and increase of it at the periphery of the cell, suggesting movement of the granules to the periphery. Lambert (289) repeated the experiments of Vas and confirmed his conclusions, except as regards the increase in the size of the cells and their nuclei.

In 1894 G. Mann (330) published an account of his now well-known series of observations. He commenced by repeating the experiments of Vas, employing, however, a special histological technique of his own in which was included staining with methyl blue and eosine and with toluidin blue. He concluded that an increase in the size of the ganglion cells and their nuclei does take place, but he could not convince himself of a shifting of the granules from the centre towards the periphery of the cell. The centre certainly became clearer, but this was to be attributed to other causes. He observed also an increased affinity of the nuclear hyaloplasm for eosine and slight diminution of the nuclear chromatin (instead of an increase as described by Vas). The nucleolus enlarged and became at the same time paler. After prolonged stimulation the nuclei began to darken slightly and to shrivel, and the chromatic substance of the protoplasm was greatly diminished. Even in extreme fatigue, however, he did not find that the nuclei were darker than the protoplasm. He also studied the cells of the motor cortex and spinal cord of fatigued dogs. In the cortex there was great diminution of the chromatic substance of the protoplasm, swelling of the nucleus and pallor of the nuclear hyaloplasm ; in the cord (lumbar region) the chromatic substance of the protoplasm was diminished in amount and pale, the nucleus was darker than the protoplasm instead of lighter, and at the same time homogeneous and shrivelled. In the retina of the dog fatigued by prolonged exposure to light, as well as in the centres connected therewith, he also observed distinct structural changes. He summed up the conclusions derived from all these observations as follows :—

During rest several chromatic materials are stored up in the nerve-cell, and these materials are used up by it during the performance of its function; activity is accompanied by an increase in the size of the cells, nuclei and nucleoli of the sympathetic, ordinary motor and sensory ganglion cells; fatigue of the nerve-cell is accompanied by shrivelling of the nucleus, and probably also of the cell, and by the formation of a diffuse chromatic material in the nucleus.

In 1895 Lugaro (238) made his important contribution to our knowledge of this subject. He reviewed the observations already recorded, and pointed out their contradictory character. He maintained that the method of experimentation of Vas could not be regarded as furnishing a comparison between the condition of repose and that of activity. On the one hand the cells of the sympathetic ganglion were in a state of normal activity, in the other they had been for a short time over-excited, or had suffered an abnormal form of excitement. His own experiments consisted of variations upon those of Vas. To secure cells in a state of rest he killed animals rapidly under chloroform, and allowed the ganglia to remain for some hours *in situ* before fixing. He confirmed the conclusion of Nissl that the chromophile state of the nerve-cell is an artificial condition, and suggested that it is produced by the sudden action of alcohol. He could not observe the changes in the chromatic substance of the protoplasm described by Vas. Variations in the quantity of this substance in different states were only very slight, and were "subject to the incertitude of subjective appreciations." Differences of chromatic intensity in the cells of the same ganglion certainly could not be exclusively attributed to differences in functional state. Even in ganglia which had been long stimulated, there could always be distinguished clear cells and dark cells, with all intermediate gradations. He summed up his conclusions as follows:—(1) Activity of the nerve-cell is accompanied by swelling of the protoplasm of the cell-body; (2) fatigue produces a progressive diminution in the size of the cell-body; (3) in moderate degrees of activity, while the protoplasm of the cell-body is swollen, the nucleus does not undergo any change in size; (4) when activity is continuous

and long protracted, the nucleus undergoes modifications analogous to those of the cell-body, but less intense; (5) the quantity of the chromatic substance in the cell-body varies especially as an individual character in relation to the size; nevertheless it is probable that the first phases of activity determine a slight increase in it, the later phases, accompanied by fatigue, a diminution and a more diffuse distribution; (6) activity of the cell determines in the nucleoli an increase of volume which gives way slowly to the reducing action of fatigue. In the same year Nissl (370) made a long communication upon this subject, in which he severely criticised most of the conclusions previously recorded. Two years before he had maintained that the different degrees of affinity presented by nerve-cells for basic stains, or differences in quantity of chromatic substance in the protoplasm, were probably due to the diverse functional states of activity and repose (360). In another paper (365), published early in 1895, he distinguished these different degrees of colourability by the terms *pycnomorphous*, *parapycnomorphous* and *apycnomorphous*, applying the first to cells which stained very deeply, the third to those which stained very faintly, and the second to those which showed an intermediate intensity of colour. He stimulated the facial nerve with the faradic current, and observed that there was afterwards a preponderance of dark cells in the nucleus of origin. He concluded that the pycnomorphous condition (which is to be distinguished from the artificially produced chromophile state in which the cell is still more deeply and very diffusely stained) represents a state of fatigue in the cell, and that the apycnomorphous condition represents a state of relative repose. Thus he believed, contrarily to Mann, that the chromatic substance accumulates in the cell during its functional activity. In his paper (370) dealing specially with this subject, however, he admits that the pycnomorphous condition must be regarded as the anatomical expression of the resting state. But he maintains that the conditions which Hodge and Mann believed to be characteristic of fatigue and exhaustion are artificially produced, and that the anatomical conditions characteristic of these states still

require to be determined. He thinks that faradic stimulation should not be used in such experiments, as it gives rise to changes which are to be attributed to chemical, thermic and traumatic irritations.

In 1896 Valenza (512) described the results of experiments upon the electric lobe of the triton. He found that direct stimulation by strong faradic currents caused a hyperchromatosis of the nuclei of the nerve-cells, accompanied in the slighter degrees by swelling, in the more severe degrees by contraction. Fatigue produced by currents of medium force never caused any alteration in the volume of the cells, of their nuclei or nucleoli. Eve (136) repeated the experiments upon the cervical sympathetic ganglia, and also made a series of control experiments. He found that rest and activity caused very little difference in the histological appearances of sympathetic nerve-cells. The only change that he could detect as the result of protracted activity was the occurrence of a slight diffuse blue staining of the cell-substance. His control experiments led him to attribute this diffuse staining to the formation of an acid in the cell and a consequent slight solution and diffusion of the basophile material. Pergens (412-413) found that in the retina of fishes the action of light caused diminution of the chromatic substance in all the strata below the molecular.

In 1898 Pugnat (394-395), from experiments (electrical stimulation) upon the spinal ganglia of kittens, concluded that activity of the nerve-cell is accompanied by increase in the volume of the cell-body and nucleus, and by diminution of the chromatic substance of the protoplasm, and fatigue by diminution of the cell and of its nucleus, and decrease in the amount of chromatic substance. F. Pick (401) stimulated the motor cortex of monkeys and cats with the faradic current in such a way as to cause unilateral contractions, thus producing fatigue of the motor cells of the cord on one side only. He found that in the fatigued cells the chromatic substance of the protoplasm was diminished and broken up into fine granules, which were placed mostly at the periphery of the cell. The nuclei were shrunken. Luxenburg (276) obtained results very similar to those of Pick by

stimulation of a crural nerve after hemisection of the cord and transverse section at a higher level. G. P. Pellizzi (410) has endeavoured to study the process of atrophy from suspension of function while the nutrition of the nerve-cells is preserved, by isolating a portion of the frontal lobe in dogs without severing the essential vascular connections. He finds that the cell-body undergoes a progressive atrophy which slowly extends centrifugally to the protoplasmic prolongations, which for a long time maintain their normal characters. The chromatic substance of the protoplasm is preserved until the atrophy of the cell is advanced. In a later paper (411) he records some very important observations upon the cells of the cœliac and mesenteric ganglia in dogs during the different stages of digestion, from which he concludes that the chromatic particles of the protoplasm become consumed during functional activity of the cell.

Giuseppe Levi (260) has studied this question from a different point of view from that of the observers already mentioned. He endeavoured to investigate by a microchemical analysis the intra-cellular products of the metabolism of the nerve-cell, and to study the qualitative and quantative modifications of these during the functional states, as had previously been done in the case of certain other tissues. His researches were made upon the 7th lumbar ganglion of rabbits. Activity was produced in the cells by faradic stimulation of the sciatic nerve. He used Hermann's solution for fixation of the tissues, and stained by Galeotti's acid fuchsine and methyl green method. These observations led to the discovery of the fuchsinophile granules of the nerve-cell, which Levi regards as a true product of metabolism. They are present in the normal cell and consist of exceedingly minute particles which are sometimes slightly elongated. They are coloured bright red by the above staining method, thus contrasting sharply with the other elements of the cell, which are stained green. They lie in the interfibrillar, unorganised substance of the protoplasm, but occur also, though only in small numbers, in the nucleus. In the resting condition of the cells (attained by section of the sciatic nerve and examination of the

ganglion after two days) these granules were diminished in numbers. On the other hand, after stimulation of the nerve they were greatly increased in numbers and in size, many of them appearing considerably elongated. The maximum was reached after stimulation for about two hours.

Levi (266) has recently made another valuable contribution to our knowledge of this subject, consisting of a study of the changes occurring in the nerve-cells of cold-blooded animals during hibernation. It has been observed by himself and Jacobsohn (223) that there are no appreciable structural modifications of the nerve-cells of warm-blooded animals associated with this state. Bühler (41), in his work on the nerve-cell, which was published shortly before Levi's paper, described certain special appearances in fresh sections of the spinal ganglia of the hibernating frog, but he did not record any observations of changes recognisable in preparations fixed and stained. Levi's studies were made chiefly upon the cells of the spinal cord and spinal ganglia of the toad. His main conclusions are as follows:—The chromophile substance diminishes greatly during hibernation; in the spinal ganglia it at the same time becomes strongly basophile; it gradually increases when hibernation terminates; during hibernation droplets of fat are present in the cytoplasm, and the interfibrillar fuchsinophile granules are diminished. He concludes, after considering the question from many points of view, that these morphological changes can only be regarded as an expression of the difference in the quantity of the functional energy that the nerve-cells are capable of displaying in the hibernating state, the great diminution of the chromophile substance corresponding to the torpor and diminished excitability of the animals during winter, its increase to the vivacity which they exhibit in spring and summer.

(12) *Physiological Regressive Changes.*

Granting that senility may be regarded as a physiological condition, there are certain nerve-cell changes constantly associated with it which we may perhaps correctly designate

by the above title. Hodge (198) studied these changes in man and the bee, and observed not only alterations in the nucleus and pigmentation and vacuolation of the protoplasm, but also a complete disappearance of a large percentage of the cells. Pugnat (397), who supports the views of Hodge, has observed in the spinal ganglia of aged animals nerve-cells profoundly altered and invaded by leucocytes. The writer and Orr (457) have described the changes observed in the cortical nerve-cells in a case of apparently uncomplicated senility in a woman aged 90. Most of the cells showed a large collection of yellow pigment in their interior, often replacing the greater part of the protoplasm. A large proportion of these cells appeared in other respects perfectly healthy, showing very clearly marked and abundant Nissl-bodies in the remaining protoplasm, and a normal number of processes. Very many of them, however, showed further changes of a disintegrative character, consisting in progressive atrophy of the protoplasmic processes, shrinkage of the cell-body and loss of its angular form, disintegration of the Nissl-bodies, and loss of their affinity for basic dyes, and disintegration of the nucleus. Finally there were left only a few stained granules representing the remains of the nucleus and Nissl-bodies, accompanied generally by some scattered granules of yellow pigment.

Many other writers refer incidentally to the pigmentary and other changes that occur in the nerve-cells in senility, but a systematic histological research upon the subject is apparently still needed.

It seems very probable that these regressive changes, which are typically seen in senility, occur to a slight extent throughout life, increasing as age advances. There seems at least to be at present no other hypothesis that will explain the presence of the occasional disintegrating cell that may be found in even the healthiest brain obtained under the most favourable conditions. Luzenberger (285) observed in the cerebral cortex of the guinea-pig cells of this nature in very limited numbers surrounded by quite normal cells. He concluded that their occurrence could not be accounted for by defects of *technique*, and that it could only be ex-

plained by supposing that in normal conditions a certain number of cells are in a regressive phase which ends in complete destruction. He described this "involution of normal life" as consisting in the homogeneous rarification of the cell with destruction of the nucleus. The writer and Orr (457) from their own observations have supported Luzenberger's hypothesis and insisted upon its practical importance. It would seem that even in the healthiest nerve-cell community there are some sickly individuals,—cells which from some cause, hereditary or acquired, have become unable to maintain a normal correspondence with their environment.

Marinesco (327) has recently expressed the opinion that nerve-cells, like all other cells, undergo, in proportion as the individual advances in age, a process of involution which causes the chromatophile elements to become reduced in volume and even to assume a powdery appearance.

(13) *Structural Features of the Nerve-Cells of different parts of the Central Nervous System.*

I shall here merely enumerate the more important references and give an abstract of the description given by the writer who seems to be the best authority upon each set of nerve-cells.

Nerve-cells of the spinal ganglia.—The structural features of these cells have been specially described by Flemming (139-140-142), Nissl (360), Dogiel (118), R. A. Fleming (145), Lugaro (244-245-253), van Gehuchten (168-169), Levi (262), van Gehuchten and Nélis (176), Ramon y Cajal (436-434), Lenhossék (281-282), Huber (212), W. H. Cox (94-95-96), Heimann (210-211). I select the description given by Lugaro. He distinguishes in the spinal ganglia of the dog five types of nerve-cell:—(1) *Clear cells of large size with small, often granular chromatic particles*, which are scattered throughout the protoplasm, but which are slightly more abundant near the periphery internal to a narrow limiting zone almost deprived of them, sometimes also more abundant near the nucleus. The nucleus is large and clear, and has

almost always only one nucleolus. Around the nucleus there is always a narrow achromatic zone. These cells are fairly numerous. (2) *Clear cells of large or medium size, with chromatic particles of irregular form, small and dense,* but larger near the periphery below an achromatic limiting zone. In these cells, as also in those of the preceding type, but in a much clearer manner, it may be observed that the single particles are connected with each other by delicate processes. The nucleus has the same characters as in the first type. These cells are the most numerous of all. (3) *Dark cells of small size with small and dense chromatic particles,* which, however, are larger around the nucleus with which they may be in contact. The clearer part of the protoplasm colours diffusely. The nucleus is diffusely coloured and contains often two or more nucleoli. These cells are somewhat numerous. (4) *Clear cells of small or medium size with very large chromatic particles,* which are small in number and confluent by means of more or less delicate processes. There is often more than one nucleolus. These cells are not numerous. (5) *Clear cells of large size, with long and coherent chromatic particles* which are confluent with each other and disposed in layers arranged concentrically around the nucleus. These cells are the least numerous of all.

Lugaro's views with regard to the arrangement of the fibrillar part of these cells have already been stated [I. 3].

Cells of the columns of Clarke.—Marinesco (306) has briefly drawn attention to the peculiar characters presented by these cells. Many of them show a peripheral disposition of the nucleus and chromatic elements confined to a peripheral ring.

The normal structural features of these cells require further investigation. Numerous instances might be cited here in which they have been described as morbid changes.

Nerve-cells of the sympathetic ganglia.—These have been recently described especially by G. Mann (330), Dogiel (116), Apolant (14), Juschtschenko (224), Eve (136), Marina (351), Brukner (65), and Marinesco (322). I take the description given by Marinesco.

The achromatic fundamental substance, or trophoplasm,

is remarkable in that it presents a variable colourability, in some instances staining in an intense manner with basic dyes, in others remaining quite colourless. The achromatic organised substance, or spongioplasm, is in the form of a network as in other nerve-cells. The meshes of this network may be wide or narrow. The chromatic substance of the protoplasm in a very large number of the cells is developed only at the periphery, leaving a more or less clear perinuclear zone. It has a granular aspect. A second type of cell occurs especially in the superior cervical ganglion. The chromatic granules are placed around the nucleus, while at the periphery of the protoplasm they are entirely absent. In a third type the chromatic elements are disseminated throughout the protoplasm, or arranged concentrically. A fourth type is constituted by certain twin cells (*cellules-jumelles*) which occur especially in the inferior cervical ganglion. They are sister cells placed in one capsule. They may be joined at one extremity, though only exceptionally. They generally differ considerably in size and in appearance.

The nerve-cells of the brain and those of the anterior and posterior horns of the spinal cord, scarcely call for special notice here, as there is probably little that could be added to the descriptions of them that may be found in the text-books already mentioned. Two excellent studies of the cells of the normal cerebral cortex will be found in the papers of Hammarberg (200) and Schlapp (488).

II. Experimental Pathology of the Nerve-Cell.

(1) *Changes following Section of the Prolongations.*

Nissl (358), in the communication in which he first described his methylene blue method, gave an account of certain changes which he had been able to observe by means of this method in the facial nucleus of the rabbit after eruption of the nerve. The report above referred to was published in 1892, but the communication itself is stated to have been made in 1890. The morbid changes, which could be seen in the cells within twenty-four hours, consisted in breaking down and disappearance of the chromatin-bodies,

beginning at a particular part of the cell. In two or three days they had proceeded much further, extending over the whole cell. About the third day the protoplasmic processes became involved, showing shrinkage and loss of their chromatin striation. By the fourth day there was a swelling of the whole cell, the contour of which at the same time often appeared as if corroded. Later the cell appeared very pale and finely granular, and the nucleus moved to the periphery, sometimes projecting from the cell-body. All the cells of the nucleus were not equally affected. Many normal cells remained beside the degenerated ones. In 1894 Nissl (362) published an account of further observations of the same kind, and described the procedure by which the lesions were produced as a new method of experimental research for the nervous system by means of which it was possible to localise the various nerve-centres. He proposed to designate this method *the method of primary irritation*. His experiments were made upon the facial and other cranial nerves, and also upon some of the peripheral nerves. The changes described were essentially similar to those just detailed. He believed that the changes were the same whether the nerve was cut, excised or torn out, the essential thing being complete and continued interruption of the connection between the nerve and its centre. They reached their height in from eighteen to thirty days. After this they were stationary for a time, and then began to be repaired. In fifty or sixty days after rupture of the facial nerve the cells that had been affected could scarcely be distinguished. Individual nerve-centres showed considerable differences in their mode of reaction.

In 1895 Vanlair (516), from the results of a series of experiments upon dogs, concluded that division of a spinal nerve is in no case followed by any alterations in the structure of the spinal cord. His examinations were made from six months to two and a half years after the operation. Later in the same year Onuf (386) published an account of his experimental investigations. His paper contains a valuable *résumé* of previous observations of a similar kind, which, however, were mostly carried out with unsuitable staining

methods. He states that his own observations were made before he knew of Nissl's work on the same subject. His experiments were made upon cats, in which he cut the anterior roots (sometimes also the posterior) of spinal nerves. He secured the cord in from three days to four weeks afterwards. He used chiefly a modification of Nissl's older magenta method. The results of his independent observations agree essentially with those of Nissl. He found that in a large number of the multipolar cells of the anterior horn connected with a cut anterior nerve-root, and also in some in the opposite anterior horn, the differentiation of the chromatophile and chromatophobe substance of the cell-body was lost, and that an appearance was produced corresponding to that described by Friedmann as "homogeneous swelling." He observed that this change began in a circumscribed portion of the protoplasm, and gradually extended to the cell-body and its processes, and that the nucleus became dislocated towards the periphery. He believed that the affected cells became completely destroyed. He described this as an acute change, which generally followed section of the nerve near the cell. He distinguished also a gradual change in which the cell assumed an appearance corresponding pretty closely to Nissl's chromophile state. It was generally produced by lesion of a motor fibre at a considerable distance from the cell.

In 1896 Ceni (73) recorded the results of a series of experiments in which he cut the spinal cord of four dogs and examined the cerebral cortex in from 7 to 110 days later. The changes he described may be attributed, in part at least, to section of the prolongations of cortical nerve-cells. He found that in preparations by Golgi's method certain of these cells presented an atrophic and varicose condition commencing at the extremities of the protoplasmic prolongations and extending gradually to the cell-bodies. The nervous prolongations were only affected at a very advanced stage. These changes were not uniformly distributed, but affected individual cells and groups of cells in various portions of the cortex. After hemisection of the cord most of the cells affected were in the cerebral cortex of the opposite side. Marinesco

(305) described the results of his observations upon the nerve-cells of the cord after section of peripheral nerves, confirming most of the conclusions of Nissl and Onuf. He divided the changes in the central end of the cut nerve and in the cell into two phases. In the first the central end of the nerve remains intact, while in the cell there is produced a *réaction à distance*, characterised by more or less complete dissolution of the chromatic elements of the protoplasm, a morbid change which he here designated *chromatolysis;* in the second there is disintegration of the trophoplasm (a term which at this time he applied to the whole of the achromatic

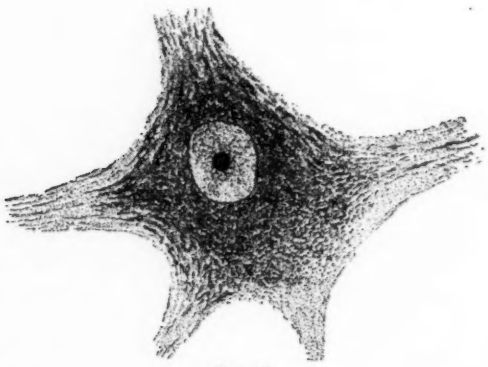

FIG. 10.

Nerve-cell of anterior horn of spinal cord of guinea-pig. Incipient chromatolysis from section of nervous prolongation. Reactive phase. Sublimate. Thionin. Compare with Fig. 1. (Lugaro 242.)

part of the cell) and changes in the central end of the cut nerve. The first is the degeneration of Nissl; the second is the degeneration of Hayem and Forel. These changes differ from Wallerian degeneration which has its seat in the peripheral end of the cut nerve. He was of opinion that some of the affected cells atrophied and disappeared. He further maintained that these changes in the nerve-cell, secondary to injury of its nervous process, have special characters which permit of their distinction from primary lesions, that is to say from those produced by the direct action of a poison.

Lugaro (242) described the results of experiments similar to those of Marinesco. He employed, in addition to thionin staining, the hæmatoxylin methods for the demonstration of the fibrillar portion of the protoplasm. He confirmed the descriptions given by Nissl and Marinesco of the changes in the chromatic part and also the inductions of the latter with regard to the behaviour of the achromatic part. His description of the changes in the large cells of the anterior horn of the spinal cord following section of the sciatic nerve is as follows:— In the first phase of alteration (reactive phase) one observes disintegration of the chromatic part, starting from the origin of the axis-cylinder; the cell otherwise preserves its normal form and the nucleus its position. With hæmatoxylin it can

FIG. 11.

Nerve-cell of anterior horn of spinal cord of guinea-pig after section of the nervous prolongation. Initiation of the degenerative phase. Sublimate. Thionin. (Lugaro 242.)

be seen that the achromatic part, in the prolongations and in the cell-body, perfectly preserves its delicate striation, which, indeed, is often rendered more evident by the disintegration of the chromophile particles. In the more advanced stage (degenerative phase) the chromatolysis extends to the greater part of the cell-body, and the nucleus is distinctly displaced. The chromatolysis advances gradually to the protoplasmic processes. In hæmatoxylin preparations the delicate striation has now disappeared from those parts of the cell-body that are most altered, and from the protoplasmic prolongations

involved in the degenerative process. When the degenerative phase is at its height, the chromatic part appears powdery, and the striation is completely lost. From an examination of the same tissues by Golgi's method, he concluded that it is only with the initiation of the destruction of the cell (degenerative phase) that alterations become recognisable with this method. In this paper he referred, but only very briefly, to the changes that occur in the spinal ganglia after section of the sciatic nerve, stating that his experiments were as yet incomplete. In October of this year R. A. Fleming (143) published an account of what appears to have been the first very complete series of observations with Nissl's method upon the changes in the cells of the spinal ganglia following section of the sciatic nerve. The chief points that he was able to establish are as follows:—The cells of the ganglia of the posterior roots undergo distinct changes as the result of nerve section or ligature, and do so at a much earlier period than the multipolar cells of the cord, beginning probably as early as the fourth day, and certainly by the seventh day. In both, one of the first changes to be observed is diminution in the size of the nucleus, sometimes also of the nucleolus; the nucleus frequently takes up an eccentric position. In both, the Nissl-granules are either smaller in size and fewer in number, or they are grouped together in large masses around the nucleus, leaving the periphery of the cell quite clear. The pericellular spaces tend to become enlarged. An actual atrophy of the cell may also occur. In the multipolar cells there is further a later phenomenon, consisting in marked disintegration of the cell-protoplasm. This change follows only at a very late stage in the cells of the spinal ganglia. It is to be noted that these observations were made upon rabbits and dogs. Colenbrander (97) described in the cells of the anterior horn of the cervical cord of the rabbit, after section of the brachial plexus, changes corresponding essentially to those observed at a lower level after section of the sciatic nerve. Lugaro (243) described his important observations upon the effects of partial mutilation of the nervous prolongations. The conditions necessary for this study he realised by section of the spinal cord at the junction

of the dorsal and lumbar portions. It is almost impossible to epitomise the conclusions of this paper. It can only be said here that chromatolytic lesions of various degrees of intensity were found above and below the point of section, and that their localisation was such as to suggest many valuable deductions regarding the connections and distribution of the various groups of cells. It should be mentioned also that the changes found in the cells of the cerebral cortex were very slight. In December of this year Lugaro (244) published a long account of his observations upon the alterations in the nerve-cells of the spinal ganglia, chiefly of the dog, in consequence of section of the peripheral or central branches of their prolongation. The first experiment consisted in the removal of a portion of skin and examination of the cells of the corresponding spinal ganglia after eighteen days. The greater number showed only more or less advanced chromatolysis, without alteration or displacement of the nucleus. The affected cells were exclusively those of the two types of large clear cell. The next series of experiments consisted in excision of the sciatic nerve at the level of the hip-joint and examination of the spinal ganglia after various periods. After twelve days more than half of the cells were affected by chromatolysis in various degrees. In the most advanced the cell-body was swollen, deformed, pale and filled with powdery remains of the chromatic part, the nucleus shrunken, deformed, displaced and deeply stained. Each kind of cell was affected excepting his fourth type. In a dog killed after thirty-nine days similar changes were observed, but there was an evident diminution in the number of nerve-cells, and a prevalence of healthy cells. In some cells the degenerative process had gone on to complete destruction, in others repair had taken place. In guinea-pigs the changes were found to be more uniform, regular and slow, the degenerative phase not manifesting itself until after the twentieth day. Section of the posterior root between the ganglion and the cord produced no distinct changes in the cells of the ganglion. The results of section of the posterior columns of the cord served to confirm the conclusion that these cells are not morphologically affected by section of the central

branch of their prolongation. The author discusses at considerable length the physiological deductions to be drawn from these observations. He concludes that it may be supposed that the sensory element resents specially the suppression of external stimuli, the motor element the suppression of the discharge of the energy which it elaborates.

In 1897 R. A. Fleming (144-145) published further accounts of his observations upon the changes in the nerve-cells of the spinal-cord and root-ganglia after section or ligature of the peripheral nerves. Marinesco (314-315), in the *Rapport* presented to the Congress at Moscow, deals very fully with the subject of secondary lesions of the nerve-cell, comparing the conclusions derived from his own observations with those of Lugaro, with which they are essentially in accord. He distinguishes three phases in the changes that occur in the nerve-cell after section of its axis-cylinder,—the reactive, the degenerative and the reparative. The time of the onset of the reactive phase varies considerably in accordance with certain conditions. After section of the hypoglossal in the rabbit, it could be observed in from two to three days; in the dog only after four or five days. He states that he has observed slight reactive changes in the cells of the spinal ganglia after destruction of the nuclei of the posterior columns and of the neighbouring sensory fibres. He gives a description of the reparative phase as observed in the hypoglossal nucleus of the rabbit after section of the nerve. It may be clearly observed in some cells by the twenty-fourth day, when reunion of the ends of the cut nerve commences to take place. The cells undergoing repair are increased in volume, and stain deeply, owing to the density and large volume of the newly-formed chromatophile elements. After forty-six days a greater number of cells have become repaired. There are now no cells in the reactive phase, but there are still many pale degenerated cells. After seventy-three days the density of the chromatic substance, and the volume of the cells undergoing repair are still further increased. After ninety days the hypertrophy of the cells has attained its maximum. After this they diminish in volume, and in an animal killed

after 111 days the hypoglossal nuclei of the two sides are indistinguishable from each other. The rapidity of the repair depends chiefly upon two factors,—the age of the animal (being more rapid in young animals) and the union of the two cut ends of the nerve. If union does not take place the number of cells that degenerate and disappear is increased. Van Gehuchten (169), in his paper, likewise communicated to the Moscow congress, gives a very minute description of these changes as observed by himself. He distinguishes two stages in the alterations that occur in the cells of the spinal cord, firstly that of the breaking down of the chromatic particles, and secondly that of their restitution. The first stage is characterised by rapidly spreading destruction of the chromatic elements from the centre to the periphery, increase in volume of the cell and displacement of the nucleus. It begins about forty hours after section of the nerve, quickly attacks simultaneously all the nerve-cells connected therewith, and lasts from fifteen to twenty days. The stage of restitution then begins, in which the chromatic elements slowly form again and the cells exhibit a pycnomorphous condition. His conclusions differ radically from those of Marinesco and Lugaro, for he maintains that the changes observed are due merely to a simple disturbance of the cell which affects exclusively the chromatic substance. In effect he asserts that the occurrence of the degenerative phase has not been proved. He believes that destruction of cells is very slight, and to be attributed when it occurs to loss of the nucleus owing to exaggerated displacement from swelling of the cell. He states that in the cells of the spinal ganglia, on the other hand, reorganisation of the cell does not occur, but complete degeneration and destruction of it. He attributes this difference between the behaviour of the sensory cell and that of the motor cell to the fact that the former is deprived of the trophic influence exercised by its physiological excitement, while the latter is not. In a later paper (170) he expresses similar opinions. He also states that he and Nélis have confirmed Lugaro's observation that the cells of the spinal ganglia do not suffer chromatolysis in consequence of section of the central branch

of their prolongation. In another paper (171) published in this year his own observations upon the effects of nerve-section are also related. In December of this year Lugaro (248) described the results of a further experimental investigation of the effects of section of the central branch of the prolongation of the cells of the spinal ganglia. He cut the posterior roots of several spinal nerves between the ganglion and the cord in two dogs, and examined the cells of the ganglia after six and twelve months respectively. In both cases the cells were quite normal in appearance. He disputed the opinion of van Gehuchten regarding the exclusive importance that is to be attributed to the trophic action of the stimuli that flow to the cell, and also dissented from the interpretation of the complete destruction of the cells of the anterior horn as a purely accidental result of nerve-section.

After this time numerous papers were published describing researches upon the localisation of nerve-centres by means of the production of secondary chromatolysis. Among these papers there are to be mentioned the following:—Van Gehuchten (172) and Marinesco (319) on the anatomy of the facial nucleus; Marinesco (323) and van Gehuchten and Buck (178) on the motor nuclei of the lumbo-sacral cord; van Gehuchten (175) on the origins of the glosso-pharyngeal and vagus nerves; Marina (351) on the centres for the movements of the pupil; Bunzl-Federn (66) on the origin of the vagus.

Van Gehuchten (173) has recently published an account of some experimental researches the results of which, to a certain extent, contradict previous conclusions of himself and others. He made a large number of observations upon rabbits, cutting various peripheral nerves, and found that in no instance was the lesion followed by chromatolysis in the corresponding cells of the cord. Some of the cells, however, were found to be in a pycnomorphous condition. On the other hand he found that section of the cranial nerves always produced chromatolysis in the cells of their nuclei of origin. He therefore concludes that the motor spinal neurons and the cranial neurons of the rabbit differ in their power of resistance to traumatism of the axon. Marinesco (323), in

his paper on the motor nuclei of the spinal cord of the dog and rabbit, refers to these observations made by van Gehuchten. He himself obtained some similar negative results after section of spinal nerves. He therefore tried the effects of excision of a large portion of the brachial plexus and of eruption of nerves. He found that the latter procedure gave a constant, rapid and very distinct reaction in the nerve-cells of the anterior horns. The alteration produced consisted in complete disappearance of the chromatic elements, while the nucleus and nucleolus were also distinctly affected. This condition he designated *achromatosis*, which, however, was not to be regarded as different from chromatolysis, but merely as a specially severe form of it due to the intensity of the traumatism. He confirmed these conclusions by further experiments upon dogs, of which an account is given in another paper (325). In still another paper (324) upon this subject he stated that the repair of nerve-cells affected by chromatolysis after section of a nerve depends upon the restoration of the continuity of the nerve. After resection or eruption of a nerve this continuity being permanently abolished there is atrophy and disappearance of the cells of the nucleus of origin.

Marinesco (322) was unable to find chromatolysis in the cells of the cervical sympathetic ganglia after section of the cervical sympathetic in the dog. D. Mirto (337), however, obtained positive results. He found that after section of the intracranial and carotid branches of the superior cervical ganglion, there was a severe and rapid chromatolysis in the cells of the ganglion, going on to complete disintegration of the chromatic substance. By the twenty-eighth day he observed diminution in the number of cells. After section of the cord (pre-gangliar fibres) the cells of the ganglion also showed chromatolysis, but it was comparatively slight in degree and in certain respects different in character. Marina (351), in his important researches upon the localisation of the centres for the movements of the pupil, found that the quantity of the degenerated cells in the ciliary ganglion was proportional to the extent of the lesions produced in the iris and ciliary processes.

Warrington (522), after section of the anterior roots of spinal nerves, observed in the corresponding cells of the cord changes similar to those found by others after section of the nerve-trunk. In animals killed from ten to twenty-four days after section of posterior roots he found, chiefly on the corresponding side, severe chromatolysis which showed marked limitation to the postero-external group of cells in the anterior horn. He found comparatively very slight changes in the nuclei of origin of the third and seventh cranial nerves after section of the nerves. It is interesting to compare the above observation upon the effects of section of the posterior roots with one made by Lugaro (243). He found that some days after section of the spinal cord at the junction of the dorsal and lumbar portions the cells of the postero-external group were specially (although not exclusively) altered below the lesion, even as far as the *conus medullaris*. On the other hand, at some little distance above the lesion all the cells of the anterior horn were intact. From these observations he drew the conclusion that these altered cells are probably not cells of the anterior root, but neurons of the second order placed on the sensory tract.

W. H. Cox (96) has given a description of the changes found in the cells of the spinal ganglia of the rabbit which differs considerably from that of previous observers. He describes two types of cells each of which becomes modified in a different way. The cells of the first type suffer chromatolysis which is distinguishable after twenty-four hours. Those of the second type are still intact up to the fourth day. Some days later, however, they present agglomeration of the chromatic granules around the nucleus. He believes that the fibrils are never destroyed, and that all the cells ultimately resume their normal structure. Marinesco (326) has recently very fully described the process of repair in the cells of the hypoglossal nucleus of the rabbit after chromatolysis produced by section of the nerve. He confirms and amplifies his previous description (314). Foà (153) concludes that repair can occur in the cells of the hypoglossal nucleus even when the ends of the cut nerve do not unite. All the cells of centre affected do not recover; some always disappear.

(2) *Changes Produced by Various Poisons (including Bacterial Toxines).*

The effects of various poisons upon nerve-cells have recently been studied by a very large number of observers, not only with the aid of Nissl's method and its modifications, but also by Golgi's method, the hæmatoxylin method and others. The earliest observations of this kind conducted with suitable staining methods appear to have been those of Nissl (359) with lead and arsenic, of which an account was published in 1892. The lesions that he observed and described were merely forms of those that are now grouped together under the term chromatolysis. He found that while in poisoning by arsenic the chromatic particles dissolve and become pale by a process of vacuolation which makes them appear riddled with holes, and in consequence broken up, in poisoning by lead there is a progressive diminution of the chromatic particles which at the same time become more homogeneous and of sharper outline. At the same time, in the achromatic part there appear granules which are quite distinct and deeply coloured in lead poisoning, pale and small in poisoning by arsenic (242). K. Schaffer (462) and Golgi (157) were also early investigators in this field.

The subject of the nerve-cell changes produced by the very numerous toxines that have been employed is probably most conveniently arranged under the individual toxines, and I shall therefore deal with it in this way discarding the purely chronological order.

As important papers dealing with the general subject of these changes, the following may be specially referred to:—Lugaro (245-256), Nissl (371-374), Marinesco (314), Goldscheider and Flatau (167), Jacottet (226), Babes (43), Nageotte and Ettlinger (380-381), and Flatau (148).

Nissl (371), on the basis of his more recent extensive investigation upon this subject, maintains that each poison gives rise to special lesions and affects certain kinds of cell to the exclusion of others. Lugaro (245) states that in primary affections of the nerve-cells from toxic action the first to alter is the chromatic part; alteration of

the achromatic part follows with a rapidity which varies with the various toxic agents and with the type of cell. Different poisons give in the same cell alterations of different type; so also a given poison in the different categories of cells.

Arsenic.—The changes produced in the nerve-cells by this poison have been described by Nissl (359-371), K. Schaffer (462), Lugaro (245), Marinesco (314-315-316), Jacottet (226), Soukhanhoff (482), and Dexler (133).

Nissl's description has already been noticed. The observations of Lugaro require special reference. He

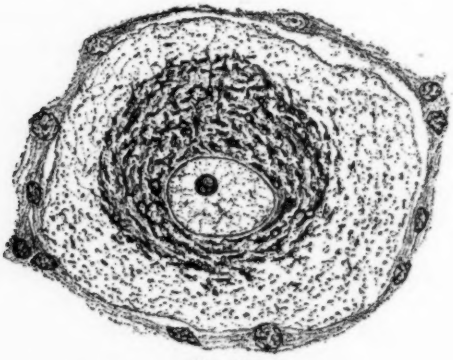

FIG. 12.

Cell of spinal ganglion (dog) showing peripheral chromatolysis. Poisoning with arsenic. Sublimate. Thionin. (Lugaro 245.)

induced slow poisoning with arsenic in two dogs which were killed after forty-three and fifty days respectively. A large number of the cells of the spinal ganglia showed peripheral chromatolysis in various stages. The achromatic fibrils were not affected, excepting at the periphery of some cells in which the morbid changes were very advanced. The chromatic particles in the cells of the anterior horn of the spinal cord appeared riddled with holes, as described by Nissl. Many of these cells were, however, normal. The achromatic part appeared as a rule intact. The small cells of the columns showed an advanced chromatolysis with

involvement of the achromatic fibrils. In tissues fixed in Flemming's solution some of the degenerated nerve-cells of the spinal ganglia and cord showed fatty granules in their protoplasm. Cox's method showed absence of rosaries on the protoplasmic prolongations and the presence of normal spinous appendages. The cells of the cerebral cortex showed relatively very slight alterations. In Cox preparations they appeared quite normal. In dogs allowed to live for fifty days after the cessation of the administration of arsenic, the cells of the spinal ganglia were mostly normal, but a few showed advanced degenerative changes, apparently having been unable to recover. Marinesco obtained a peripheral chromatolysis in the cells of the spinal ganglia, a more diffuse change in those of the cord.

Lead.—The poisonous effects of the salts of this metal upon nerve-cells have been studied especially by Nissl (359-371), K. Schaffer (462), Lugaro (245), and Jacottet (226).

The observations of Lugaro again demand special note. In the cells of the spinal ganglia of four dogs slowly poisoned with lead acetate, he found, instead of peripheral chro-

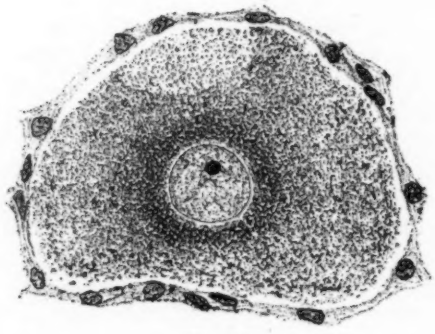

FIG. 13.

Cell of spinal ganglion (dog) with advanced diffuse chromatolysis. Severe poisoning with lead. Sublimate. Thionin. (Lugaro 245).

matolysis as in arsenic poisoning, a diffuse disintegration of the chromatic particles and progressive decolourisation of the

resulting granules, accompanied by disappearance of the achromatic fibrils. The protoplasm appeared clear, homogeneous and scattered over with extremely fine granules. The nuclei were also more or less distinctly altered. The cells of the cerebral cortex likewise presented these changes, but in a less marked degree. In preparations by Cox's method these cells appeared normal, except in one dog in which the chromatolytic changes were specially pronounced. In this animal many of them presented a condition of varicose atrophy.

Silver Nitrate.—Donaggio (103) has found in dogs killed by administration of large doses of nitrate of silver a peculiar change in the cells of the anterior horns of the spinal cord, more especially in the external and median groups. The chromophile particles of the protoplasmic prolongations were faintly stained, while the body of the cell presented an appearance closely resembling the pycnomorphous condition of Nissl. Many of the other cells of the cord showed advanced chromatolysis. While the cells of the cortex also presented this change, they showed practically no varicose atrophy with Golgi's method.

Phosphorous.—The effects of poisoning by this substance upon nerve-cells have been investigated by Sarbò (484), and more recently by Rossi (439). The latter gave daily injections of solutions of phosphorous in oil to three dogs, producing death in from six to fifteen days. Most of the nerve-cells of the Rolandic area showed only very slight disintegration of the chromatic particles. In some, however, there were more marked changes, in consequence of which they appeared as if broken in pieces, while their cytoplasm contained a powdery detritus. Many of the cells of the cord, more especially those of the anterior horn, showed advanced chromatolysis. It is surprising that this writer makes no reference to the question of the occurrence of fatty changes in the nerve-cells of these animals. In a case of poisoning by phosphorus in the human subject, described by Elkins and Middlemass (137), very decided fatty degeneration was proved to exist in the cortical nerve-cells, involving both protoplasm and nucleus.

Malonnitril.—Goldscheider and Flatau (164-165-167) have observed disintegration of the Nissl-bodies and deep staining of the chromatic substance of the nucleus in the cells of the spinal cord of animals poisoned by this substance. Injection of hyposulphite of soda, by which it is possible to arrest the symptoms of malonnitril poisoning, was followed by restoration of the cells to their normal appearance within three days.

Alcohol.—The changes produced by this substance have been investigated experimentally by Vas (511), Dehio (126), Berkley (22-25-26-27), Marinesco (314-315-316), Jacottet (226), &c.

Dehio observed slight disintegrative changes in the chromatic part of the cytoplasm, and staining of the achromatic part, in many of the cells of Purkinje of rabbits and dogs killed by acute alcoholic poisoning. Berkley (22-27), in chronic alcoholic poisoning in rabbits, observed some dissolution of the Nissl-bodies in the cortical nerve-cells only in the neighbourhood of obstructed vessels. In preparations by his modification of Golgi's silver method he observed marked and widespread changes in the dendrites, consisting of varicosity and atrophy, and structural alterations or complete loss of many of the gemmulæ. Marinesco described various forms of chromatolysis in the cells of the spinal cord in chronic poisoning in the dog. Jacottet observed similar changes in the cells of the cord and spinal ganglia.

Strychnine. — Goldscheider and Flatau (164-166), in poisoning by this substance, found in the nerve-cells of the cord changes similar to those that they have described in experimental tetanus.

Toxine of Tetanus.—The nerve-cell lesions caused by the toxic products of the tetanus bacillus have been studied experimentally by Marinesco (308-314-315), Chantemesse and Marinesco (99), Goldscheider and Flatau (164-166-167), Babes (43), Courmon, Doyen and Paviot (80), Vincenza (509), &c.

Marinesco has observed in some of the nerve-cells of the anterior horn of the spinal cord of guinea-pigs, subjected

to the action of tetanic toxine, lesions different in character from any that he has found in other intoxications. The animals were killed some time before death would naturally have supervened, and the cord was removed at once and placed in fixing solution. In guinea-pigs allowed to die from the effects of the toxine the characteristic lesions were not seen. The altered cells show two quite distinct parts. One is darkly and opaquely stained, and its normal structural features are scarcely recognisable. It is placed upon that side of the cell which gives origin to the axis-cylinder process, which itself appears granular and intensely stained. The protoplasmic processes given off from this part show an irregular and even sinuous contour. The other portion of the cell-body preserves an almost normal appearance, as do also the protoplasmic prolongations arising from it. The nucleus is generally enlarged and somewhat diffusely stained. He states that Nissl and Beck have described similar lesions in experimental tetanus. He maintains that it is necessary to distinguish two independent phenomena in nerve-cells subjected to the action of the tetanic poison, one a result of the chemical combination of the poison with the cellular protoplasm, and the other due to the wearing out of the cell from excessive functional activity. He agrees with the conclusion of Goldscheider, that the tetanic poison does not exercise upon the nerve-cell a simple exciting action, but induces a chemical transformation which exalts the excitability of the motor substance. Goldscheider and Flatau give a different description of the changes in experimental tetanus, a fact which is to be accounted for by an essential difference in the mode of experimentation. They state that tetanus poisoning in rabbits causes characteristic changes in the cells of the anterior horns, consisting in an increase in the size of the nucleolus together with pallor of it, increase in size of the Nissl-bodies and crumbling of them, and lastly fine granular disintegration of the Nissl-bodies along with enlargement of the whole cell. They found that the injection of tetanus anti-toxine retarded these cell-changes, and caused a more rapid return to normal.

Chantemesse and Marinesco found that simultaneous injection of tetanus toxine and anti-toxine resulted in no appreciable symptoms, but some modifications were recognisable in the nerve-cells. Cournon, Doyen and Paviot, from experimental results of their own, have endeavoured to discredit the observations of Marinesco, denying that tetanus toxine produces any alterations in the cells of the anterior horns. Vincenza, using Golgi's method, found varicose atrophy of the cells of the cerebral cortex.

Toxine of Rabies.—The nerve-cell changes produced by rabies have been studied experimentally by Golgi (157), Marinesco (314-316) and Caterina (86). In 1894 Golgi described in rabbits inoculated with the virus of rabies, various alterations in the form and structure of the nerve-cells. Some were slightly swollen, transparent and faintly stained. Others presented vacuolation and considerable increase in volume. He also described a vesicular degeneration in which the cell was swollen to several times its normal size; and a granulo-fatty degeneration which presented a very advanced phase of the morbid process. Preparations by his own black reaction method showed progressive atrophic changes beginning in the protoplasmic prolongations and invading the cell-body. Some of the axis-cylinders presented varicose swellings. Marinesco observed severe peripheral chromatolysis and occasional vacuolation in the nerve-cells of the cord of rabbits which had died from rabies. Caterina found similar changes in the guinea-pig.

Toxine of Bubonic Plague.—Lugaro (246) in two rabbits and a guinea-pig killed by inoculation of the virus of bubonic plague found severe chromatolysis of the nerve-cells of the cord and spinal ganglia. The achromatic portion of the protoplasm was affected. The nuclei were shrunken and obscured, presenting the acute homogeneous change described by Sarbò. Babes (42-43) found similar changes in guinea-pigs and mice. He states that the bacilli of plague are occasionally to be observed within the nerve-cells.

Diphtheria Toxine.—In 1895 Crocq (78) described in the

nerve-cells of rabbits killed by injections of cultures of Löffler's bacillus changes corresponding to a severe type of chromatolysis. The cells of the anterior horns of the cord were first affected, and afterwards those of the lower part of the medulla oblongata. Ceni (74) described the occurrence of varicose atrophy of the nerve-cells of guinea-pigs and rabbits in experimental diphtheria. Babes (43), who has also studied these changes experimentally, mentions the interesting fact that he has found that the injection of large quantities of diphtheria anti-toxine is capable of producing distinct alterations in the cells of the anterior horn of the spinal cord in rabbits. Mouravieff (348), in guinea-pigs subjected to the action of diphtheria toxine, observed well-marked changes confined to the nerve-cells of the anterior horn of the spinal cord. They consisted of chromatolysis, principally peripheral, vacuolation of the cell-body and its prolongations, a corroded appearance of the edges of the cells, and sometimes loss of the nucleus. In a later paper (349) he described some comparative observations upon the effects of streptococcal infection, and also of the combined action of diphtheritic and streptococcal toxines.

Toxines of Bacillus Botulinus.—Marinesco (310-314-315) has studied the changes produced in the nerve-cells of lower animals by these toxines. He observed severe degrees of chromatolysis, generally commencing peripherally. As the morbid changes advanced there was destruction of the achromatic fibrils and formation of vacuoles. The cells of the spinal cord and medulla oblongata were chiefly affected. Kempner and Pollack (234) have found similar changes in the nerve-cells, and have further observed the slow restoration of the cells to normal under the action of the specific anti-toxine.

The following papers still require mention here :—Müller and Manicatide (352) upon poisoning by acids; Berkley (28) upon ricin poisoning; Pandi (409) and Vas (511) upon poisoning by nicotine, &c.; Daddi (111) and Pandi (409) upon cocaine poisoning; Sarbò (484) and Saratschow (461) upon morphia poisoning; Mourek and Hess (355) upon the effects of numerous different poisons; Köster (235) upon

carbon bisulphide poisoning; Borri (63), poisoning by carbonic oxide and by sulphuretted hydrogen; Döllken (132), aluminium; Gabei and Antinori (194), urine, ammonium carbonate, &c.; Crisafulli (83) and Wright (523), potassium bromide; D. Mirto (338), neurine; Brauer (59) and Dotto (128), mercury; D. Mirto (336) *latirismo*.

(3) *Changes produced by other Experimental Lesions.*

Many of the changes dealt with in this subsection (more especially those occurring in inanition, pyrexia, uræmia, and anæmia) are of the greatest practical importance, as they tend to complicate the pathological picture in cases of nervous disease in the human subject, and therefore require to be recognised and discounted before conclusions of any value can be formed regarding the relation of morbid appearances in the nerve-cells to the special clinical symptoms.

Inanition.—The changes in the nerve-cells in this condition have been studied by A. Monti (291-292), Pernice and Scagliosi (406), K. Schaffer (465), Lugaro and Chiozzi (258), Ganfini (186), Daddi (112), and Müller and Manicatide (352).

Monti, using the method of Golgi, observed varicose atrophy of the protoplasmic prolongations. Pernice and Scagliosi observed in fowls deprived of water alone complete disappearance of the chromatic substance and vacuolation; with Golgi's method deformity of the cell-bodies and fragmentation of the dendrites. K. Schaffer observed in the nerve-cells of the cord in rabbits chromatolysis, vacuolation, and the homogeneous change of Sarbò in the nucleus. The lesions were specially severe in animals deprived of water as well as of food. Lugaro and Chiozzi, from observations upon dogs and rabbits killed after various periods of starvation, concluded that the nervous elements remain for a long time intact, or only show slight alterations in the chromatic substance. These alterations are, however, aggravated during the few days preceding death. The achromatic substance and the nucleus may also become

involved. Varicose atrophy of the protoplasmic prolongations is always slight, and is not preceded by loss of the spinous processes. They think that the lesions observed are not an expression of atrophy of the nervous elements, but that they are the result of a true auto-intoxication, which becomes rapidly aggravated in the last days of life through simultaneous alterations in the structure of the various viscera. Ganfini found in the rabbit chromatolytic changes in the cells of the cord, but not in those of the cerebral cortex. Daddi has studied the subject in dogs, and obtained results corresponding very closely to those of Lugaro and Chiozzi. He thinks, however, that the changes depend upon general denutrition, and not upon auto-intoxication.

Insomnia.—Daddi (110) in experimental insomnia in dogs found especially in the cortical nerve-cells more or less advanced chromatolysis, swelling of the cell-body, and vacuolation of the protoplasm. The method of Golgi also revealed varicose atrophy of the protoplasmic prolongations and disintegration of the cell-body. The nucleus also presented marked structural changes, and in many instances was displaced to the periphery of the protoplasm. Agoştini (1) independently carried out similar experiments and observed practically the same morbid changes.

Ablation of the Supra-renal Bodies.—Ettlinger and Nageotte (379) observed in dogs subjected to this experimental lesion advanced chromatolysis and formation of fissures in the nerve-cells of the cord. Similar, but less pronounced changes were found in the cells of the cerebral cortex. Donetti (113) in rabbits and guinea-pigs found this lesion followed by peripheral and concentric chromatolysis, going on frequently to complete destruction of the cells. The changes were most advanced in the medulla oblongata.

Experimental Uræmia.—Acquisto and Pusateri (16) in dogs which died as the result of ligature of the ureters, found varicose atrophy affecting specially the pyramidal cells of the cerebral cortex, and various phases of chromatolysis, often very advanced, in the cells of the cerebral cortex and

spinal cord. Sacerdotti and Ottolenghi (459), after ligature of the ureters or nephrectomy in dogs and rabbits, found changes in the nerve-cells essentially the same as those described by the preceding observers.

Experimental Anæmia.—Sarbò (485) found that one hour after ligature of the abdominal aorta the nerve-cells of the spinal cord showed disintegration of the chromatic substance of the cell-body, and "homogeneous swelling" of the nucleus. Marinesco (305) observed peripheral chromatolysis of the nerve-cells of the cord five to six hours after ligature of the abdominal aorta. The nucleus remained central. In a later paper (307) he described these changes more fully. In advanced stages he found the nucleus altered. The achromatic network of the protoplasm was disintegrated and replaced by vacuoles and even cavities. In another paper (314) he regards the morbid changes as essentially the result of œdema of the nerve-cell. Ballet and Dutil (35) observed changes very similar to those described by Marinesco. They found that commencing dissolution of the chromatophile elements could be recognised after the abdominal aorta had been compressed for only a few minutes. In advanced stages they often found the nucleus eccentric in position. Jatta (227), from the results of experiments upon rabbits, dogs and cats, has questioned the accuracy of the conclusions of previous observers. His work has been severely criticised by Lugaro, and it is doubtful if any importance is to be attached to it. Soukhanoff (481), using the method of Golgi, observed varicose atrophy of the protoplasmic prolongations of the cortical nerve-cells after ligature of both carotids.

Experimental Elevation of Temperature.—Goldscheider and Flatau (164-165-167) studied the influence of the elevation of the body-temperature in rabbits (by placing them in a thermostat) upon the nerve-cells of the spinal cord. They found that marked changes occurred as soon as the temperature of the animals was raised to 43° C. (109·5° F.). In preparations by Nissl's method the Nissl-bodies had almost completely disappeared. The cell-body was swollen, homogeneous and stained bright blue. It contained some

minute granules, and presented also the appearance of a thread-network. The dendrites were pale blue and swollen, somewhat varicose and shadow-like. The nucleus was also more or less altered. Temperatures of from 41·7° to 42° C. (107-108° F.), if maintained for about three hours, produced similar but less distinct changes. The cells returned to normal in from two to three days. Lugaro (250) studied

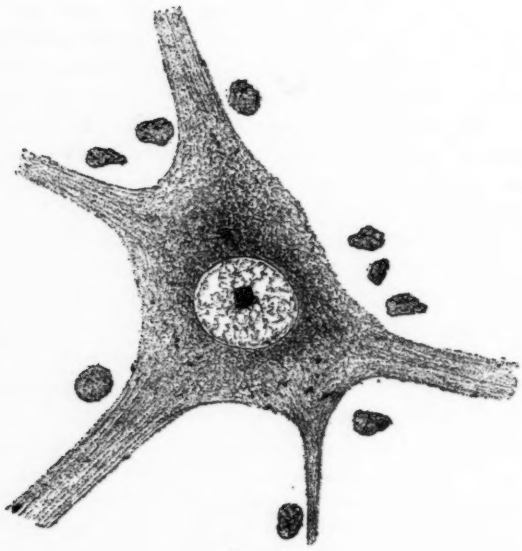

FIG. 14.

Cell of anterior horn of spinal cord of rabbit. Experimental elevation of temperature. Compare with Fig. 1. Sublimate. Thionin. (Lugaro 250.)

these pyrexia changes throughout the nervous system in the rabbit and dog. Summing up the results of his observations he states that the nerve-cells of animals of which the temperature has exceeded 43° present the following characters:—Profound disintegration, very marked dissolution of the chromatic part; integrity of the achromatic part,

the reticulo-fibrillar structure of which is often rendered more evident than in the normal state; integrity of the external form and of the morphological characters of the protoplasmic and nervous prolongations; integrity of the nuclear membrane and reticulum, diminution of the colourability (with thionin) of the acidophile portion of the nucleolus, and slight modifications of form in its chromatin particles. A feature of the morbid change is that (unlike chromatolysis from most other causes) it is diffused throughout all the cells in an almost equal degree. Moxter (335), in experiments upon the effects of the local application of heat after trephining of the cord in rabbits, found that with temperatures between 40·5° and 41·5° changes occurred in the nerve-cells of the anterior horns only after twenty-two and a-half hours. Marinesco (327), who has recently also made an experimental enquiry into this subject, thinks that the alterations resulting from artificial elevation of temperature may be divided into three groups, according to the height and duration of the abnormal temperature. The first type of alteration results from the action of a maximum of heat (reaching about 47°) and a minimum of its duration (forty minutes), and consists in a dissolution of the chromatic substance only at the periphery of the cell. The second results from the action of a less degree of heat (the temperature of the animal varying during the experiment from 43° to 45°), extending over a considerably longer time, and consists essentially in those lesions described by the previous observers, except that the chromatophile elements are not always completely dissolved. The third results from the action of a temperature of about 44° for several hours, and consists of a still more severe lesion. The cell stains very deeply, has an opaque appearance, and has lost all trace of chromatophile elements. There has in this instance probably been a coagulation of the protoplasm, a lesion which is equivalent to the death of the cell. Ewing (135) records some experiments upon rabbits, which he states bear out completely the conclusions of Goldscheider and Flatau regarding the structural changes produced. The bearing of these experimental observations upon the

study of nerve-cell changes in the human subject has been incidentally alluded to by several writers (162-346a) including those mentioned above, but the point is one that seems still to require careful investigation. It is obvious that in the human subject the action of the elevated temperature must in the great majority of instances be complicated by that of toxines generated in the course of the particular disease with which the pyrexia is associated. In other words, pyrexia-changes in the nerve-cells of the human subject must as a rule be combined with chromatolysis of toxic origin.

Death from cold.—D. Mirto (339), in pups killed by the action of cold, found peripheral chromatolysis and other changes in the nerve-cells throughout the nervous system. The pyramidal cells of the cerebral cortex were those most affected. Goldscheider and Flatau (167) could find no changes in the cells of the cord in rabbits which died as the result of subjection to low temperatures.

Death by electricity.—Corrado (98), in dogs killed by shocks of from 10 to 30 ampères, found very severe lesions affecting the nerve-cells. The cell-bodies showed erosions, notchings, lacerations and mutilations; the cell-outline was more or less diffuse, as if melted, or plainly irregular. Occasionally there was an appearance suggesting that part of the protoplasm had been burst out from one side of the cell by the sudden evolution of gas. The chromatic substance had undergone dissolution. Vacuolation was frequent. Changes in the nucleus were for the most part slight. With Golgi's method the protoplasmic processes showed varicose atrophy and numerous fractures, with disintegration of the fragments. Some of these processes, but especially the apical, tended to have a spiral appearance, suggesting contraction.

Among other experimental lesions of which the effects upon the nerve-cells have been studied are the following:—Cerebral abscess (Barbacci, 30), abdominal and thoracic traumatism (Parascandalo, 414), cerebral traumatism (Luzenberger, 285), slow asphyxia (Dotto, 130), intestinal autointoxication (Cristiani, 69, Alessi, 21).

(4) *Proliferative Capacity of the Nerve-cell.*

This question, which is one of considerable physiological and pathological importance, was for a long time a subject of dispute. It has, however, been recently most thoroughly worked out by Giuseppe Levi, thanks to whom it now rests upon a satisfactory scientific basis. Most of the previous observations upon which were founded assertions of the capacity of the nerve-cell to proliferate are necessarily of doubtful accuracy, since the histological methods employed did not permit of a distinction being clearly made between nerve-cells and neuroglia-cells. It was not until Levi had analysed the constitution of the resting nuclei by means of staining with Biondi's reagent that trustworthy criteria for such a distinction were provided.

Friedmann (138), Caporaso (77), Vitzou (514), and Tedeschi (504) maintain that they have observed the regeneration of nerve-cells; Friedmann (138), Marinesco (301), Sanarelli (477), and Tedeschi (504) believe that they have observed karyokinetic figures in nerve-cells either during repair or irritation. Marinesco (301), Sanarelli (477), Tirelli (494), and Monti and Fieschi (294) have been unable to obtain evidence that the nerve-cell is capable of regenerating.

Golgi (157) observed karyokinetic changes in the nerve-cells in experimental rabies, but thought that they represented rather a regressive process of kariolysis than a true karyokinesis. Valenza (512) was unable to observe any evidence of karyokinesis in the nerve-cells of the electric lobe of the triton after stimulation or cauterisation. In 1895 Stroebe (476) published a review of the literature of this subject.

In 1896, Levi (261), after the publication of his first paper upon the normal structure of the nucleus, briefly related some observations made with Biondi's staining upon healing aseptic wounds of the cerebral cortex of the guinea-pig. Among the abundant karyokinetic figures found especially in the healthy tissue surrounding a wound, many were in nuclei which could be proved to be those of nerve-cells from their staining reactions as well as from other

evidence. A complete account of his researches upon this subject was only published last year (264). In this more recent paper he states that the object he specially set before him in his researches was to study the process of karyokinesis in nerve cells, admitting that it occurs, and to observe what deviations from the normal it presents. The methods of observation employed were those already indicated, but experiments were made upon the spinal cord as well as upon the cortex. He states the criteria which served him for the distinction of the nerve-cell nuclei from those of neuroglia and other cells. He found that the process of karyokinesis in the nerve-cells has, in its early phases, certain special features dependent upon the peculiar structure of the nucleus. It is doubtful if it would serve any purpose to endeavour to describe this process here. Anyone who desires to understand the matter must necessarily consult the original paper, and follow the description of the process with the aid of the beautiful coloured plates by which it is illustrated. Levi has only been able to observe karyokinesis in the medium-sized and small pyramidal cells of the cortex of the guinea pig. He could not find it in very highly differentiated nerve-cells, such as the large cells of the cord and brain. Although he has never observed complete division of a nerve-cell, he is inclined, from the advanced stages of karyokinesis that he has observed, to think that it can occur. It is probable, however, that such multiplication of nerve-cells is simply a reaction to the stimulus that has affected them and that it does not lead to a stable regeneration. In favour of this view is the fact noted by several observers that the proliferation of the nerve-cells is most active from the second to the fifth day, afterwards diminishing gradually and ceasing about the twentieth day. He thinks that very highly differentiated nerve-cells, when affected by a stimulus, undergo degeneration instead of attempting to multiply. Their reproductive capacity has become lost in favour of that of fulfilling their special function. The index of this loss of reproductive capacity is probably the paucity of nuclein, which, as has been seen, diminishes with the higher differentiation of the cells.

(5) *Post-mortem Changes in Nerve-Cells.*

This subject, the importance of a thorough knowledge of which to the neuro-pathologist must be obvious, has recently been studied experimentally by several observers. Tirelli (497) in his lengthy work upon the chronology of the death of the elements of the nervous system, which is chiefly of medico-legal interest, states that nine hours after death there can be observed a diffusion of the chromatic substance into the achromatic part of the protoplasm. The cell-body then assumes a finely granular aspect throughout. According to Colucci (89) the chief alterations are a diffuse granular disintegration of all the cell-elements excepting the nucleolus, pale and turbid staining with methylene blue, loss of affinity for this stain in tracts of the prolongations, rupture of the protoplasm in various directions in many cells, &c. Neppi (377) studied the cadaveric alterations in the cells of the anterior horn of the spinal cord of the dog, using sublimate fixation and thionin staining. He could not find distinct changes until forty-eight hours after death. They consisted chiefly in dissolution of the chromophile substance (the particles of which first showed badly defined outlines and then diminished affinity for the stain) and diffuse colouration of the nucleus. The nucleolus was only affected at a very late period. The cells tended to shrink and not to swell as in chromatolysis. Barbacci and Campacci (29) have made a very elaborate series of observations upon rabbits killed by bleeding and afterwards kept at a uniform temperature of 22° C. After various periods they examined different portions of the central nervous organs by the methods of Nissl (sublimate-thionin modification), Cox and Marchi. Their description of the changes observed is full of minute details of which it is impossible to give an accurate epitome. They state that the first alteration as a rule consists in the progressive paling of the chromatic particles. These next generally break up into fine granules which become smaller and smaller, giving the protoplasm a characteristic powdery look; sometimes, on the other hand, there is a fusion of the particles into irregular masses. Later the protoplasm assumes a pale, finely granular appear-

ance and tends to lose its regular outline. The nucleus undergoes a dropsical change which leads to its rupture and shrinkage. It then appears as an irregular homogeneous mass which stains deeply. The nucleolus only at a very late stage becomes pale, irregular in form and displaced. In preparations by Cox's method there is detachment of the gemmulæ, erosion and breaking across of the protoplasmic processes and cell-bodies. Later the whole element assumes a very characteristic powdery aspect. Giulio Levi (269) has also carried out a vary careful investigation into this subject upon rabbits, using the sublimate-thionin method. His results differ from those of the preceding observers, chiefly in regard to one point. He describes an initial hyperchromic phase, or a condition of abnormally deep staining of the chromatic elements which precedes that of pallor and fragmentation. França (150) has obtained in guinea-pigs results which are essentially in agreement with those of previous observers. Tirelli (498) has recently made a comparative study of the appearances of cadaveric and pathological changes in the brain of the rabbit with the aid of the rapid silver method. His results are not at all in accord with those obtained by Barbacci and Campacci with Cox's method, to which, however, he does not refer. He finds that even somewhat advanced putrefaction does not deprive the nerve-cells of their characteristic aspect in silver preparations. An excellent account of these cadaveric changes has been given by Ewing, both in his preliminary communication (134) and in his comprehensive monograph upon ganglion cells (135). In his first paper he notes especially deep diffuse staining of the nucleus at an early stage, shrinkage of it and of the nucleolus in advanced stages; granular subdivision of the chromophilic bodies and reticulum, without actual loss of chromatic substance, which gives to the cell-body a characteristic uniformly granular appearance. In his more recent work, he deals with the subject still more fully and describes some experimental observations upon the rabbit. In addition to the above changes he mentions the occurrence of vacuoles in the protoplasm which he believes to be one of the most con-

stant of *post-mortem* products. The writer and Orr (457) have described and figured these *post-mortem* changes as observed in the cortical nerve-cells of the human subject in methyl violet preparations, and have pointed out how they are to be distinguished from genuine chromatolysis.

III. Types of Morbid Change affecting the Nerve-cell.

(1) *Chromatolysis.*

The term "chromatolysis," introduced by Marinesco (305), implies, strictly speaking, merely disintegration of the chromatic particles of the protoplasm—breaking up of the aggregations of granules that form the Nissl-bodies and gradual disappearance of the individual granules, accompanied in transition stages by their diminished affinity for basic dyes. But it has been frequently used in a wider and more general sense, namely, to indicate the whole series of changes in the constituent elements of the cell, of which dissolution of the chromatic particles is merely the first that is recognisable. The term has therefore in the meantime its narrower and its wider senses. I use it here only in its narrower sense.

The various causes of chromatolysis, and the different appearances that it presents, have probably already been sufficiently illustrated in the preceding section. It remains for me here merely to briefly notice certain general facts and opinions regarding the morbid process, and to refer to its occurrence in the human subject.

Chromatolysis may be peripheral, perinuclear, or diffuse; partial or complete. It may occur as an acute or as a chronic change. Comparatively little, however, is known about its chronic forms, owing chiefly to the greater difficulties which they present in the way of experimental investigation. A typical example of chronic chromatolysis is that which occurs in senile involution of the nerve-cell.

The mechanism and significance of chromatolysis have given rise to much discussion. The following papers contain special reference to this subject:—Lugaro (242-250),

Marinesco (312-314-327), van Gehuchten (170-173), Goldscheider and Flatau (164-165-167), Ballet and Dutil (35). In 1896 Lugaro (242) stated that the exact mechanism of chromatolysis was still uncertain and obscure. The matter can scarcely be said to stand otherwise to-day. Regarding the significance of chromatolysis much has recently been written. It is to be remembered that the function of the Nissl-bodies is still in dispute, and it is therefore only to be expected that the significance of their disintegration should also be a matter of difference of opinion. In the paper just referred to Lugaro maintained that alterations of the chromatic part do not represent more than a reaction of the cell to a disturbing force and are reparable; while on the other hand alterations of the achromatic part are to be regarded as degenerative and irreparable. This view, which had been foreshadowed by Marinesco (305), has since been very generally accepted as in accordance with the facts. Goldscheider and Flatau, from their observations upon the occurrence of chromatolysis in experimental pyrexia and in malonnitril poisoning, were led to maintain that the Nissl-bodies have no great importance either for the vitality or the functional activity of the cell, and that chromatolysis has little significance as a pathological change. An animal with its motor cells thus markedly altered was still able to perform all kinetic functions. Lugaro (250) states that he cannot accept these opinions in their entirety. According to his own observations, although the motor functions may be preserved apparently intact in experimental pyrexia, with the progress of the alterations there is a motor weakening. The chromatic part fulfils its functions through its chemical, not through its morphological, structure. Its quantitative and structural integrity is not essential for motor function, yet its progressive dissolution causes progressive weakening of that function. The morphological conditions necessary to function consist in the structure of the achromatic part and in the connections between the various nervous elements, determined by the disposition of the cellular arborisations. While these morphological conditions are

preserved, the possibility of functional activity is also preserved, but its intensity depends upon the quantity of the chromatic substance existing in the cell. This substance has, without doubt, an important and indispensable part in the functional metabolism of the element. Marinesco (327) has supported Lugaro's opinion in this matter, and has expressed himself even more emphatically with regard to the importance of the chromatophile elements for the vitality and functional activity of the cell. His own experimental observations have led him to conclude, contrary to the opinion of Goldscheider and Flatau, that cells that have reached a state of absolute achromatosis cannot recover.

Chromatolysis has been observed in the human subject in a very large number of different morbid conditions. Indeed it is now known that it occurs in some degree in a proportion of the nerve-cells of almost every individual dying a natural death. Even in non-nervous diseases it is very commonly an extensive and well-marked morbid change in the cells of the cerebral cortex, spinal cord, &c. In such cases it is to be attributed to the action of toxic substances generated in the course of the particular disease, to pyrexia, terminal auto-intoxication, or to local vascular lesions (286). At the same time abundant evidence has now been accumulated of the special incidence of chromatolysis in various forms of nervous disease. A list of recent papers dealing with the morbid changes in the nerve-cells in various diseases in the human subject is appended to this section. In practically all of these papers that describe the results of examinations with the method of Nissl, as most of them do, there will be found recorded the occurrence of disintegration of the chromatic elements of the protoplasm.

(2) *Achromatolysis or Plasmolysis.*

These terms have been applied by Marinesco (314) to one of three different morbid changes which have been recognised by him and others to occur in the constituent elements of the achromatic part of the cytoplasm, either simultaneously with or consecutive to chromatolysis in the

narrower sense. He describes it as consisting of a molecular disintegration of the achromatic substance. It is to be observed that he does not restrict the terms to disintegration of the formed or fibrillar portion of this substance. Loss of the primitive fibrils and their replacement by powdery granules is, however, practically the only visible alteration in achromatolysis. It was Lugaro (242) who first described this alteration, and he has since given several minute descriptions of it as observed in various experimental lesions, more especially in hæmatoxylin preparations.

(3) *Coagulation of the Achromatic Substance.*

This is the second lesion of this part of the cytoplasm distinguished by Marinesco (314). He describes it as consisting in the coagulation, and probably the chemical transformation, of the achromatic substance into a colourless mass of vitreous aspect. It is most typically seen in the cells of the spinal cord after ligature of the abdominal aorta.

(4) *Intense Colourability of the Achromatic Substance.*

This is the third morbid change distinguished by Marinesco (314) in this substance. It is displayed especially in preparations by Nissl's method and its modifications, and has been noted by several observers, more especially in poisoning by arsenic and antimony, and in Landry's paralysis.

(5) *Varicose Atrophy.*

This term has been applied to certain morbid appearances sometimes to be observed in the nerve-cells in preparations by Golgi's method and its modifications. It consists in the presence of irregular swellings or varicosities in the course of the protoplasmic prolongations, partial or complete disappearance of these prolongations and shrinkage and deformity of the cell-bodies. It is certain that such abnormal appearances in Golgi preparations may be the result of genuine pathological changes in the form of the cell; but it is equally certain that many of its slighter manifestations, more especially varicosities, may be, and in many published

descriptions have been, of a purely artificial character. It is to be borne in mind that the presence of varicosities on the protoplasmic prolongations is normal in the fœtus. Loss of the gemmulæ has sometimes been referred to as a distinct morbid alteration, but it can scarcely be separated from varicose atrophy. The subject is one of considerable importance and therefore I give a somewhat detailed account of its literature.

In 1893 Colella (91) described the occurrence of varicose changes in the nerve-cells in general paralysis. In 1894 Golgi (157) described similar alterations in experimental rabies. They resembled those that he had described in chorea in 1874. Ceni (71) found them in secondary degeneration of the cord, Andriezen (12) in alcoholic insanity. Klippel and Azoulay (4) in general paralysis and melancholia. The last-named authors stated that the alteration began as an abrasion of the gemmulæ, or as an agglutination of them, and that it spread gradually from the periphery of the protoplasmic prolongations towards the cell-body.

In 1895 Berkley (22) described changes similar to those just mentioned in chronic alcoholic poisoning in rabbits. In another paper (24) he recorded the observation of the loss of a large number of the gemmulæ in secondary dementia, Ceni (72) described varicose atrophy in the cells of cerebellum after lesions of the cord, Tirelli (495) in the cerebrum of general paralytics, and of epileptics dying in *status epilepticus*, Pernice and Scagliosi (405) in diphtheritic infection, Monti (290) in experimental embolism, and (291) in inanition.

In 1896 Demoor (107) described the production of varicosities upon the protoplasmic processes by the action of morphia, chloral and chloroform, as well as by that of prolonged electrical stimulation, and their disappearance on the return of the elements to normal conditions. Berkley (26) gave a further account of the varicose changes in the cortical nerve-cells of rabbits subjected to chronic alcoholic poisoning, describing especially a distinct diminution in the size of the cells, a shrinkage of the vast majority of them, swellings of the dendritic processes with disappearance of

the gemmulæ, and roughening of the stronger processes and to a less extent of the cell-bodies. At the same time, he drew attention to certain "normal inequalities or varicosities in the construction of the dendrons." In another paper (27) he described the changes produced by experimental acute alcoholic poisoning as revealed by his modification of Golgi's silver method, mentioning specially irregular tumefaction of the protoplasmic processes, and considerable loss of the lateral buds, with or without such tumefaction. Dotto (128) described varicose atrophy in chronic poisoning by perchloride of mercury, and (129) by quinine and ergotinine; Ceni (73) in the cells of the cerebral cortex after section of the spinal cord in dogs, and (74) in diphtheritic poisoning (chiefly experimental). Lugaro (242) drew attention to the difficulties that surround the employment of Golgi's method in pathology. He stated that alterations simulating varicose atrophy were readily produced by defects of fixation, such as commonly resulted from the use of bichromate of potassium either alone or with osmic acid. He recommended the use of Cox's solution, even with which, however, the pieces should not exceed 1 cm. in thickness. He attributed to such imperfect fixation the results obtained by Demoor, whose experiments he had repeated with totally negative results. All these reservations, however, did not prevent the acceptance of varicose atrophy as a real anatomical alteration, as it had been observed in experimental material examined with the most rigorous technique. Its exact value could not yet be established. It could be excluded, however, that it expressed a simple disturbance of the nutrition of the element, or an initial alteration. It probably represented a final destructive process which revealed itself first in the most delicate parts. Ramon y Cajal (428) also drew attention to the production of these varicose changes by defective methods of examination. Acquisto and Pusateri (16) observed varicose atrophy of many of the cells of the cerebral cortex in acute experimental uræmia.

In 1897 Sacerdotti and Ottolenghi (459) confirmed the immediately preceding observation. Dotto and Pusateri (131), from a study of the cortex in a case of cerebral

hæmorrhage, supported the opinion of Lugaro that varicose atrophy represents not an early, but a late phase of alteration in the nerve-cells. Lugaro (245), in his

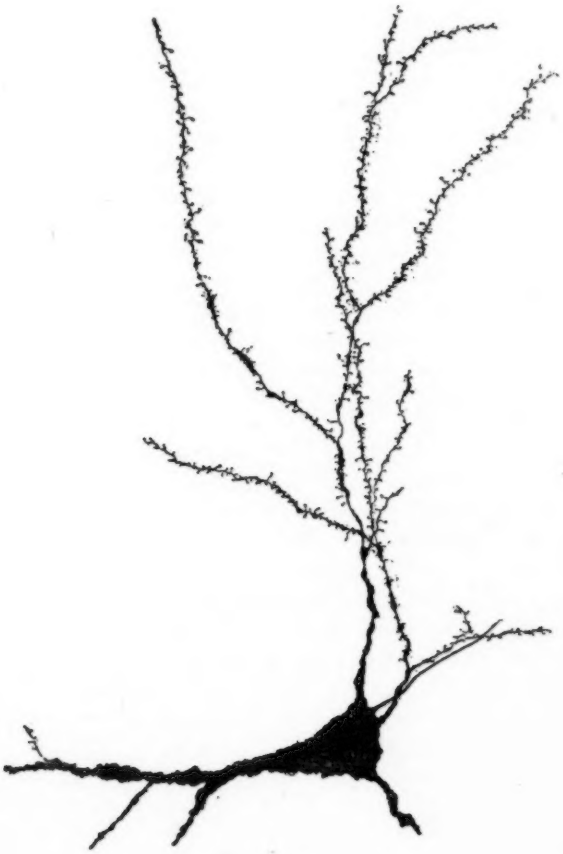

FIG. 15.

Pyramidal cell of cerebral cortex of dog. Severe lead poisoning. Cox's method. (Lugaro 245.)

investigations of the changes in poisoning by arsenic and lead, obtained further important evidence in support of

this conclusion. He found that even when there are distinct cytological alterations the external form of the nerve-cell, as revealed by Cox's method, may appear quite intact. When alterations did appear they affected specially the cell-body and large protoplasmic trunks, and notwithstanding their presence the fine branches and the gemmulæ might be preserved. He expressed himself as more than ever doubtful of the pathological value of swellings in the form of a rosary, preceded by loss of the spines and invading the protoplasmic prolongations progressively. He had been able to prove that such varicosities could be produced in enormous numbers by the employment of fixatives that are not very energetic and of too thick pieces of tissue. Further, he believed that mechanical maltreatment of the pieces and their subjection to the action of the air could produce similar modifications. In support of the latter point, he referred to the fact that Ramon y Cajal (428-429) had been able to demonstrate that the numerous varicosities which appear in preparations by the Ehrlich-Dogiel method in all prolongations of the nerve-cells are due to the altering action of the air. Lugaro adds that sometimes in normal preparations treated with all possible precautions, there are to be observed some prolongations with the characters of the so-called varicose atrophy, which are certainly due to some cause of alteration that has escaped notice. Lugaro and Chiozzi (258), in their observations upon the changes resulting from inanition, found that varicosity occurred only at a very late stage of the cellular alteration, and that it was not preceded by disappearance of the spinous appendages.

In 1898 Monti (293) described, in the nerve-cells of animals subjected to inanition, varicose atrophy proceeding regularly from the extremity of the dendrites towards the cell-body. He maintained that the dendrites were the first to undergo alteration in inanition, and that there exists a perfect correspondence between this alteration and chromatolysis, both of which were to be observed in disturbance of the nutrition of the nerve-cell. This paper elicited from Lugaro (249) a very vigorous criticism, which, however, was not

directed solely against the views just mentioned. He maintained that the appearances described were nothing more than artificial products depending upon errors of technique. In his observations upon experimental pyrexia (250), he found that the extreme chromatolysis thereby produced is not accompanied by any alterations of the protoplasmic prolongations in Cox preparations. Batty Tuke (503) has recently accepted as demonstrated the loss of the gemmulæ of the dendrons under the action of disease. It must be replied that, however probable such an occurrence is, the evidence that has yet been adduced in support of it is not decisive. Peters (413a) concludes that the gemmulæ are diminished in correspondence with the degree of intellectual decadence in the insane. Wright (523) describes varicose changes in the cortical nerve-cells in accidental and experimental poisoning by potassium bromide. Soukhanoff (481) describes gross changes in the form of the protoplasmic prolongations in experimental cerebral anæmia, and Corrado (98) in death by electricity. The writer and Orr (457), following essentially the technique advocated by Lugaro, have observed in the human brain in various pathological conditions occasional varicose changes corresponding to those recognised as genuine by that authority. Demoor (107-108) Stefanowska (474), Querton (417), Manouelian (300) and Odier (389), have described varicosities of the protoplasmic processes, with or without disappearance of the gemmulæ, as evidence of contraction in various functional modifications of the nerve-cells. On the other hand, Azoulay (3) has been unable to obtain such evidence, and Lugaro (252), by injection of the vessels of the living brain with Cox's fluid, has also obtained results contrary to the conclusions of these observers.

(6) *Varicose Hypertrophy of the Axis-cylinder Process.*

This is another morbid appearance that may not infrequently be observed in preparations by Golgi's method. It consists, as the name that has been given to it implies, in globular, fusiform or irregular swelling in the course of the axis-cylinder process. It was first recognised by Golgi in

1874 in chorea, and afterwards in rabies (157). Colella (91) believes that it is sometimes a primary change in general paralysis. In 1896 Lugaro (242) expressed the opinion that it was improbable that the condition could be separated from lesions of the cell-body, but at the same time seemed to doubt if it was a genuine pathological alteration at all. Numerous incidental references to these varicosities are also made in other papers, but the subject seems to be one that still requires to be placed upon a sound scientific basis. The writer and Orr (457) have described and figured a more gross change in the axis-cylinder processes in the human brain in various pathological conditions, and have expressed the opinion (which they believe is in agreement with that of Lugaro) that simple swellings in the form of a rosary are not necessarily pathological alterations at all. Illustrations of these varicose changes will also be found in the text-book of Clouston (100).

(7) *Pigmentary or Yellow-globular Degeneration.*

Neurologists in this country have been made familiar with the subject of pigmentary degeneration of nerve-cells more especially through the writings of Bevan Lewis. On the Continent comparatively little importance is attached to this transformation, about the only recent writer who deals with it at any length being apparently Colucci, who, however, objects to the term "pigmentary" and adopts that of "yellow-globular degeneration." The nerve-cell pigment in normal conditions has already been considered in another section (I. 5), which should here be referred to by the reader.

Pilcz (392), in his important work on nerve-cell pigment, states that the pale yellow variety continues to increase with age in the human subject. This statement is confirmed by many other observers. Hutchison (209) does not accept Bevan Lewis's statement that the accumulation of pigment is "invariably a witness to byegone functional hyper-activity." He has found such accumulation to be the rule rather than the exception in the human brain. He believes that pigment is specially increased in renal disease, and that it is not more abundant in the insane than in the

mentally sound. The views of Colucci (89) upon this subject do not appear to be so well known in this country as they deserve to be. He objects to the term "pigmentary degeneration" on the ground that it is not proved that the globules are true pigment granules, and that it is probable that they are really a product of metabolism in the cell. He thinks that all the elements at the spot are probably involved in the transformation, as every trace of the original structure disappears. He describes the appearances that the globules present in normal and pathological conditions. The criterion of degeneration is especially their appearance in portions of the cell that are not normally provided with them, as at the base of the protoplasmic prolongations and in the peripheral zone. Occasionally the nucleus becomes affected. The yellow globules undergo various transformations, the most common being fatty and pigmentary degeneration. In the latter they may become quite black. He thinks that yellow-globular degeneration is most marked in slow dementias such as epileptic dementia and general paralysis. Lugaro (245), in experimental lead poisoning in the dog, observed in the cells of the spinal ganglia and cerebral cortex the occurrence of yellow pigment granules, which are normally wanting in these elements in this animal. Adolf Meyer (344) has described the various manifestations of pigmentary degeneration in the giant cells of the para-central lobule. Cristiani (68), Turner (493) and Lord (289a) have published papers in which pigmentary changes are described as observed in the brains of the insane. Bevan Lewis (272), in the second edition of his important text-book, has recently given a very full account of his views regarding "pigmentary or fuscous degeneration." He holds to his opinion that excessive pigmentation is a witness to byegone functional hyper-activity, and does not notice the criticism of Hutchison. He maintains that the fuscous state is not truly a degeneration of the cell-protoplasm, although it may be accompanied by it, or be its immediate cause. He gives a minute description of the various phases of excessive pigmentation, which he divides into three stages or periods, namely, those of over-activity,

diminished activity and absorption. Epileptic insanity and general paralysis are the forms of mental disease in which he has found the nerve-cells most prone to this morbid change.

It remains to be added that pigmentary degeneration is obviously identical with one or more of the slowly progressive or chronic forms of chromatolysis, and that the fact of real importance in the morbid alteration is not the accumulation of an abnormal quantity of yellow granules, but the associated destruction of the spongioplasm and trophoplasm. The present state of our knowledge of the subject does not, however, permit of a definite conclusion as to which of these changes is the primary one.

(8) *Vacuolation.*

Vacuolation of nerve-cells has recently been the subject of special papers by Campbell (84) and Skae (458), and it has also been considered somewhat fully by Colucci (89), van Gehuchten and Buck (178), Bevan Lewis (272), and Ewing (135). Its occurrence has further been incidentally described by Daddi (109) in passive congestion, by Piccinino (399) in a case of Landry's paralysis, Ceni (75) in experimental acute septic meningitis, by Corrado (98) and Fish (147) in death by electricity, by Marinesco (320) in paraplegia, by Berger (53), and Anglade (15) in general paralysis, by Soukhanoff (482) in arsenic poisoning, by Köster (235) in carbon bi-sulphide poisoning, and by Sarbò (485) and Marinesco (307) after ligature of the abdominal aorta, and by many others.

It would serve little purpose to give an outline of the views expressed regarding vacuolation in each of these publications, for it is the plain fact that no satisfactory investigation upon this morbid change has yet been recorded. The truth of this contention is fully recognised by van Gehuchten and Buck, who, after reviewing the literature of vacuolation and stating practically all that is definitely known about it, conclude that further research is required on the subject before precise statements can be made regarding it.

The important facts that have been established may be

summed up in a few words. Vacuolation may affect either the nucleus or the protoplasm, or both; it consists in the formation in the cell-substance of one or more, small or large, non-colourable globules which are probably most commonly of a fluid character, although the observations of Corrado demonstrate the possibility of their sometimes being vacuoles in the stricter sense of the term; when fluid in character, they may almost certainly be composed of essentially different substances in different instances. They are undoubtedly composed of fatty matter in certain instances, but the assertion that they are, as a rule, of this nature has not been satisfactorily proved, and is probably erroneous. The various causes that determine their formation, the processes of their development, the associated changes in the chromatic and achromatic substances of the protoplasm and in the various constituents of the nucleus, and their pathological significance, have yet to be determined.

(9) *Fatty Degeneration.*

The possibility of the occurrence of fatty degeneration in nerve-cells as in other cell-elements seems now to be satisfactorily demonstrated, although at one time it was denied. Elkins and Middlemass (137) observed it in an extreme form, affecting both protoplasm and nucleus, in a case of phosphorus poisoning. It seems certain that vacuolation in some of its manifestations depends upon the formation of fatty globules; it has been noted also that in pigmentary degeneration the yellow globules are capable of undergoing a fatty metamorphosis. Lastly, Lugaro (245) and others have observed fat granules in nerve-cells affected by chromatolysis.

(10) *Displacement of the Nucleus.*

In advanced stages of chromatolysis (in the wider sense) the nucleus tends to become displaced or dislocated to the periphery of the protoplasm. It may come to project beyond the surface of the cell, and occasionally, according to some authorities, may even be completely extruded. Lugaro has maintained that the true significance of this displace-

ment of the nucleus is that the achromatic reticulum, which normally holds the nucleus in its generally central position, has become destroyed.

(11) *Homogeneous Degeneration of the Nucleus.*

In 1895, Sarbò (485) described in the cells of the spinal cord, affected by chromatolysis after ligature of the abdominal aorta, a peculiar change affecting the nucleus and characterised by a homogeneous aspect, deep staining with methylene blue, and atrophy. He designated it *acute Homogenesirung mit atrophie.* This expression cannot be rendered literally in English, but probably it is sufficiently represented by "homogeneous degeneration." Many writers in describing similar appearances of the nucleus in various morbid conditions identify them with this change described by Sarbò. Among these writers may be mentioned Colucci (90), Donaggio (103), and Lugaro (246), the last of whom briefly indicates the parts that the acidophile and basophile constituents of the nucleus appear to play in the morbid alteration. The pathology of the nucleus of the nerve-cell has still to be written, and until this is done it is impossible to say whether or not we are justified in regarding "homogeneous degeneration" as a special morbid change.

(12) *Invasion by Bacteria.*

While it is certain that bacteria exert their morbid influence upon nerve-cells practically only by means of the easily diffusible toxines that they generate, the observation of the occurrence of these organisms within the cell-body is one of considerable interest and importance. Such observations have recently been made by Nissl (371), Piccinino (399), and Babes (43). Piccinino found a diplococcus in the acutely degenerated nerve-cells of the spinal cord in a case of Landry's paralysis, while Babes observed the specific organisms in nerve-cells in plague, leprosy and other infective diseases.

(13) *Loss of Nerve-Cells.*

Death and total disappearance is the fate of a certain percentage of nerve-cells affected by acute primary lesions. Whether or not the same result occurs in secondary lesions

is a matter of dispute. Chronic forms of chromatolysis, such as that which occurs in senility, must also, it is evident, result in the loss of large numbers of nerve-cells. The question of the manner in which the dead nerve-cells are removed is one that has given rise to some dispute. Marinesco (314) thinks that proliferated neuroglia cells conjointly with leucocytes act as destroyers of degenerated nerve-cells. Bevan Lewis (272) believes that certain large cell-elements of the neuroglia are the all-important elements in this connection. Turner (491) describes leucocytes as attacking, destroying and removing nerve-cells in the cerebrum in senile insanity and other morbid conditions. Pugnat (397) has described the invasion and removal of degenerating nerve-cells by leucocytes in senility, an occurrence which he attributes to the diminished resisting power of the nervous elements. Nissl (368), in his paper upon general paralysis, maintains that the nuclei to be observed upon the degenerating nerve-cells are only those of neuroglia cells, and that leucocytes are never to be observed in this position. Lugaro (254) supports Nissl's view from his own observations. He states that he has searched in vain for leucocytes in the cortex of paralytics and in that of the rabbit in meningo-encephalitis. Neuroglia-cells are to be observed grouped about the pyramidal nerve-cells in the healthy state. Their nuclei are sometimes so planted on the nerve-cell as to simulate a lymphoid element in the act of penetrating it. The writer and Orr (457) have stated that in many cases of secondary dementia it can be satisfactorily demonstrated that about 50 per cent. of the cortical nerve-cells have entirely disappeared. The loss of nerve-cells which occurs in the spinal cord and posterior root ganglia after amputations has recently been described by Campbell (85).

(14) *Developmental Arrest.*

As loss of nerve-cells is the most important fact in the pathological anatomy of secondary dementia, so arrest of development of nerve-cells at some stage in their growth is the most important fact in that of certain forms of idiocy

and imbecility. Hammarberg (200) made a most complete examination of nine brains from such cases, the results of which furnish most convincing evidence upon this point. A good account of his work is given by Ireland (218). Bevan Lewis (272) has found developmental arrest of nerve-cells only in epileptic idiocy and has failed to find it in simple forms of congenital defect and deaf mutism. Köppen (230) observed arrest of development of nerve-cells in one case of idiocy and paucity of cells in another. Ireland (218) refers to a case observed by the writer in which there was a zone of developmental arrest running through the layer of large pyramidal cells throughout both hemispheres.

(15) *Other Types of Change described.*

The above list by no means exhausts all the forms of morbid change that have been described in the nerve-cell. "Granular disintegration or degeneration" is still described by Bevan Lewis (272) as a separate pathological entity. It is a change revealed by his fresh method, and the description that he gives of it leaves little doubt in the writer's mind that it is to be identified with various manifestations of chromatolysis, including its acute forms and chronic senile form. Colucci (89) describes granular degeneration but recognises its identity with chromatolysis. It is to be mentioned also that Nissl (367-368) in 1896 described four disease-forms of the cortical nerve-cell in general paralysis; and more recently (374) he has drawn special attention to an acute alteration affecting the whole nerve-cell,—body and processes,—and all the cells of the cortex simultaneously.

Index of papers in Bibliography containing descriptions of nerve-cell changes in various morbid conditions in the human subject.

Landry's paralysis, 314, 315, 298, 388, 56, 399, 455, 184.
Locomotor ataxia, 311, 44, 170, 467, 468, 469, 464, 221, 270, 244, 342, 232, 233, 181, 402, 453, 347, 311, 383, 297, 385.
Bulbar paralysis, 314, 315, 517.
Infantile paralysis, 333.
Peripheral neuritis, 143, 144, 145, 303, 305, 307a, 314, 321, 473, 480, 37, 242, 123, 31, 32, 163, 287.

Epidemic cerebro-spinal meningitis, 61.
Paraplegia, 174, 521, 320.
Tetanus, 183, 454, 217, 403, 114.
Diphtheria, 43, 405, 74.
Rabies, 478, 86.
Acute chorea, 187.
Pellagra, 440, 441, 438.
Paralysis agitans, 86, 36, 181.
General paralysis, 367, 368, 53, 34, 15, 4, 495, 81, 82, 19, 20, 195, 57, 193, 416, 89, 272, 68, 91, 92, 222.
Acute alcoholism, 207, 507.
Acute insanities, 207, 70, 5, 6, 457, 100, 502, 19, 272.
Epilepsy, 76, 329, 220, 442, 495, 415, 89, 272, 68.
Mental confusion, 33, 6.
Secondary dementia, 296, 24, 457, 413a, 272, 6.
Idiocy and imbecility, 200, 13, 230, 218, 100, 272.
Pernicious anæmia, 58, 185.
Fevers, 327, 162, 346a, 124, 317.
Various non-nervous diseases, 134, 209, 457, 508, 86, 135, 286, 60, 208.

IV.—Addendum upon Physiological and Pathological Deductions.

Although the purpose of this digest is to give an account of observations relating only to the morphology of the nerve-cell, it has seemed to me that the importance of a number of the structural details that are described cannot be correctly appreciated except in the light of certain closely related physiological questions that are now the subject of controversy. For this reason I add a brief account of recent views upon some of these questions.

The present position of the Theory of the Neuron.

As is well known, the neuron theory has always been opposed by Golgi. Recently he has firmly maintained his position in the matter, and has promised a further demonstration of the existence of his diffuse network (159-160). The numerous alleged observations of direct connections between nerve-cells that have lately been made have also a certain weight of argument against the doctrine of the neuron, but the really serious attack that has been made upon this doctrine, which was generally thought to be so firmly established, is that for which Apáthy is primarily responsible. His very remarkable conclusions regarding the

structure of the nervous system of certain invertebrates, of which an account has already been given (Section I., 9), are in certain respects supported by the observations of Bethe, and they have been accepted by Nissl (374-375). There are now many who have been led to believe through the writings of these authorities that the neuron theory has been proved to be false. It is becoming evident, however, that this is not the view that is going to be taken by those authorities whose judgment in such a matter is most valued by the great majority of neurologists. Among these authorities Lugaro (256), and Lenhossék (283) have already spoken in a very decided manner. Lugaro's contribution to the controversy takes the form of a long *recensione* of the paper in which Nissl (374) announced his acceptance of Apáthy's teaching and declared his belief that the neuron theory is no longer tenable. It would be impossible to give an accurate outline of Lugaro's closely reasoned and most valuable critique. It should be read by all who desire to understand the true factors in this controversy, and more especially by those who have hastily concluded with Nissl that the neuron theory has received its death blow. Lugaro maintains that the observations of Apáthy and Bethe do not warrant the general conclusion that nerve-cells are connected with each other by means of their primitive fibrils, and considers that Nissl has been too precipitate in adopting this view. Even admitting Apáthy's demonstration of a continuous network formed by these fibrils outside the nerve-cell in certain invertebrates, such an arrangement has not yet been proved to exist in vertebrate animals, while there is the strongest histological evidence that it does not. Lenhossék (283), whose article is a critical review of a paper by Bethe (50), can find in the discoveries of this observer and also in those of Apáthy nothing that contradicts the neuron theory. He thinks that Apáthy's conception of the central neuropil as a true diffuse elementary network has not been conclusively demonstrated. In any case it is but the view of a single observer. It is entirely erroneous to cite Bethe's observations in support of Apáthy's views, for Bethe has himself declared that he has been unable to con-

vince himself of the existence of a true network in *carcinus mænas*. With regard to Bethe's now famous experiment upon this animal, Lenhossék denies that in it the conditions have been fulfilled that would give to its results any surprising character.

Among other recent papers dealing with the theory of the neuron the following may be mentioned:—Tanzi (499), Schäfer (471), Golgi (158), Marinesco (302), Renaut (450-451), van Gehuchten (168), Soury (483), Klippel (232), Barker (62), Dercum (127), and Goldscheider (161).

Function of the Protoplasmic Prolongations.—There are two opposing views at present held with regard to the function of the protoplasmic prolongations. Firstly, there is that of Golgi, according to which they have a merely nutritive function without subserving that of nervous conduction; and, secondly, there is that supported by the large majority of other authorities according to which this portion of the the nueron is essentially related to nervous conduction. Of recent papers dealing with this controversy probably the most interesting are those of Golgi (159) and Lugaro (251). The former found in his pericellular reticulum a new and important argument in support of his opinion, while the latter criticised Golgi's paper and defended the more generally accepted view. Several observers, on the ground of the observation of varicosity of the protoplasmic processes advancing centripetally in certain morbid conditions, have maintained that these processes must have a nutritive function. The fallacious character of such evidence has been repeatedly maintained by Lugaro (see especially No. 249).

The Law of Dynamic Polarisation.—The enunciation of this law has very commonly been attributed to Ramon y Cajal (419), but van Gehuchten (168) has maintained, evidently upon good grounds, that it was really he who was the first to advance it. According to this law or theory (which has been very widely accepted), as originally stated, the nervous current is cellulipetal in the protoplasmic processes and cellulifugal in the axis-cylinder process; in other words, the dendrites are the organs of reception of

the nervous impulse, the axon is the organ of their distribution and application. In order to obviate certain objections to this theory, and to permit especially of its being applied to the case of the cells of the spinal ganglia, both Ramon y Cajal (432) and van Gehuchten (168) have proposed to slightly alter its formula. The former thinks that there may be a direct passage of the nervous current from a dendrite to an axon arising from it, and that we should therefore speak of the nerve-current as *axipetal* (instead of cellulipetal) in the dendrites, and *dendrifugal* (instead of cellulifugal) in the axis-cylinder process. Van Gehuchten regards the large protoplasmic processes and the cell-body as forming together the true cellular body, and believes that the conduction is here indifferent, occurring in any direction. Tanzi (500) thinks that Cajal's new theory is unnecessary, and is inclined to admit the correctness of van Gehuchten's view, but insists more upon the fact of the fibrillar structure of the prolongations, and therefore of the possibility of conduction in them in both directions. He points out that Cajal's imagined correction of the law of dynamic polarisation does not remove its essential defect, which consists in the necessity of considering as gigantic dendrites the peripheral sensory fibres coming off from the cells of the spinal ganglia, although they are medullated and do not differ in any respect from the nervous prolongations. Lugaro (247) considers that neither of the new interpretations are necessary, since the fibrillar structure of the prolongations admits of a double conduction and of the separate existence of dendrite and axon in a common trunk, such as that given off by the cells of the spinal ganglia.

Function of the Chromatic and Achromatic Parts of the Cytoplasm. — There are at present two principal views regarding the function of the chromatic substance of the cytoplasm. According to the first, which is supported by van Gehuchten, Nissl, Lugaro, Lenhossék, Cajal, and many others, it is "a material of reserve destined to serve for the nutrition of the nervous elements" (168). According to the second, which has been advanced by Marinesco (305),

"it serves to augment the difference of potential of the centrifugal nerve wave." Marinesco has very fully explained his views upon this point in his *Rapport* presented to the Moscow Congress (314). He admits that the chromatic substance plays at the same time a considerable *rôle* in the nutrition of the cell. There seems every reason to believe that both of these views are essentially accurate.

Lugaro (250) expressly states that he believes that the chromatic substance has an important and indispensable part in functional metabolism of the nerve-cell. Bevan Lewis (272), in stating that "Lugaro regards Nissl's granules, so far as function is concerned, as having a passive rôle," has unwittingly misrepresented the view of the Italian neurologist, whose use of the term "passive" in this connection has reference not to function, but to the morphological relationship of the chromatic substance to the achromatic fibrils (Lugaro, 239-250). The contention of Goldscheider and Flautau (165), that the Nissl-bodies have no vital importance for the nerve-cell, has been fully answered by Lugaro (250) and Marinesco (327).

The histological evidence that the chromatic substance is utilised during functional activity of the nerve-cell was for long of a somewhat unsatisfactory kind, but Pellizzi's recent observations upon the changes in the cells of the cœliac and mesenteric ganglia during digestion (see Section I., 11) furnish what is probably the most important evidence that has yet been obtained in confirmation of the conclusion of Mann formulated in 1894.

The great majority of authorities are agreed that the fibrillar portion of the achromatic substance subserves the function of conduction of the nervous wave. Cajal (433), however, considers that we are not warranted in restricting the performance of this function to a single structural element. The non-organised portion of the achromatic substance is believed by Marinesco (322) to be the seat of intense chemical phenomena, and of such importance for the nervous element as to be appropriately designated the *trophoplasm*. That this substance is the seat of important metabolic changes is amply confirmed by other observers,

more especially by Giuseppe Levi from his study of the fuchsinophile granules.

Functions of the Cell-Body.—The cell-body in virtue of the fact that it contains the nucleus is clearly the trophic centre for the whole cell-element. That this is so is fully borne out by experimental evidence. But there seem to be the strongest reasons for believing that the cell-body has also other special functions to perform, although there are some authorities who would limit its rôle to that just stated. According to the law of dynamic polarisation, the nervous wave is received by the terminations of the dendrites, carried to the cell-body and thence to the axon. Now, according to the views of the best authorities on the subject, this nerve-wave, arriving at the cell-body, is there essentially modified and reinforced before being discharged by way of the axon. This is the teaching of the two Continental neurologists who have given most attention to the question, and who, from the vast range of their experimental observations, have the best title to be heard upon it. I refer, of course, to Marinesco and Lugaro.

Marinesco's theory of the function of the chromatophile elements, already noticed, implies that in the cell-body the nerve-wave has its potential energy largely increased in virtue of the chemical changes which occur in these elements. He further states (314), "it is due in part to the modifications which the chromatophile elements impress upon the nervous wave that the nerve-cell becomes a source of energy. . . . . The mechanical conception of the nervous phenomena which I have just formulated in this work is in harmony with many physiological and pathological phenomena. In fact physiology teaches us that the nerve-cell is a source of energy, and this source of energy, according to my view, is due at least in large part to the modifications which the chromatophile elements impress on the nervous wave which traverses the cell." In other papers he is no less explicit in maintaining that in the body of the nerve-cell there takes place a liberation of energy which serves to augment the nerve current as it traverses the cell. Lugaro's opinion upon this subject has also been often and clearly expressed.

I need quote only one passage :—" From facts regarding the structure of the cell-body it is seen that this is not a simple conductor but a modifier of the nervous wave, whence the necessity of the afferent current traversing it in every case before passing in a modified form to the efferent prolongation " (247a).

The recent teaching of Gowers (182) upon this point is doubtless well known to the reader. His opinion that the fibrils " can merely conduct through the cell-body as they do elsewhere in their course," in other words that the cell-body does not generate nerve force, is one that is doubtless shared by other neurologists, but the fact remains that the great weight of authoritative opinion is at present entirely against it.

The alleged amœboidism and plasticity of the nerve-cell. —Attention has recently been directed at considerable length to the present position of this important question by the *British Medical Journal* (67). I can only refer to it here very briefly. A large number of observers, chiefly belonging to the French and Belgian schools, have maintained, partly from experimental evidence, partly upon purely theoretical grounds, that the protoplasmic prolongations of nerve-cells exhibit functional contractility. They maintain that contraction of them occurs in fatigue of the nerve-cells, and that it is capable of explaining sleep, hysteria and many other cerebral phenomena. Lugaro (252), on the basis of a series of entirely new experiments, denies that the processes of nerve-cells contract to any important extent in different functional states, that on the other hand it is only the gemmulæ that undergo movements of retraction and propulsion, and that not retraction of these processes, but general expansion of them, is characteristic of sleep. His experimental results, obtained with the aid of an incomparably superior technique, certainly go far to prove that the histological evidence of contraction of the protoplasmic processes obtained by other observers is entirely fallacious. In connection with this subject it deserves to be mentioned that the fresh method of Turner (492) gives a beautiful demonstration of the elasticity of the nerve-cells. But it is, of

course, impossible to affirm that this elasticity postulates anything as to their functional plasticity.

It may be useful to give here an index of the papers included in the list of literature which deal with this subject :— 518, 489a, 445, 127, 274, 398, 120, 121, 228, 424, 433, 107, 108, 3, 417, 188, 189, 451, 389, 474, 125, 356, 215, 252, 168, 67.

Primary and secondary lesions.—Marinesco (305-312-314) has maintained that the changes that occur in a nerve-cell after section of its prolongation (secondary lesions) have a special character which permits of their being distinguished from those that occur from the direct action of a noxious agent (primary lesions). In secondary degeneration the nerve-cell always comports itself in a uniform manner. The alteration begins by disintegration of the chromatic substance in the neighbourhood of the cone of origin of the axis-cylinder process, and gradually extends to the greater part of the cell-body. At an advanced stage the nucleus is often displaced to the periphery. The cell may undergo repair, or it may atrophy and disappear. In primary degeneration the alterations are specially characterised by their variable multiplicity and by their gravity. The chromatolysis may be partial or complete, peripheral, perinuclear or diffuse, &c. The achromatic substance and the nucleus tend to be involved, and repair is then rendered impossible.

Further experience of secondary lesions has shown that the alterations are not so characteristic as was at first proposed. Some observers have been unable to see any differences in the two classes. Nevertheless, there seems to be little reason to doubt that secondary lesions have features distinctive from primary lesions. If present investigation cannot fully confirm Marinesco's contention, those of the future may be trusted to do so.

Degeneration by transmission, or secondary neural atrophy.—Some discussion has lately taken place regarding to what extent the degeneration of one neuron involves the degeneration of another to which it normally transmits its functional impulse. Jelgersma (219) and Klippel (232) have described the occurrence of such "degeneration by trans-

mission." Marinesco (302-306) maintains that trophism is a reflex action propagated from one neuron to another, and that continued functional excitation is indispensable to trophic activity in the nerve-cell. He points to examples of what he terms "secondary neural atrophy" of nerve-cells in the human subject as the result of degeneration of the cells from which they normally receive stimuli. K. Schaffer (464) has attributed the degeneration of the cells of the anterior horn of the spinal cord in amyotrophic tabes to degeneration of the collaterals of the posterior roots, and the consequent loss of the stimuli normally received from them. He has also observed degeneration of these cells in cases of hemiplegia from cerebral lesions. Van Gehuchten (169) attaches great importance to the trophic influence that one nerve-cell exercises over another. He records some experimental observations which go to show that after section of the sensory nerves the histological alterations do not confine themselves to the first neurons, but affect also the second which are in connection with them. He thinks that this degenerative process may pass on to neurons of the third order, and even be transmitted to the motor neurons. Berger (53) found no change in the cells of the cord three weeks after extirpation of the motor region of the brain. Acquisto and Pusateri (17), in a case of amputation of the leg, observed after twenty-nine years degeneration and loss of nerve-cells in the corresponding area of the motor cortex. Warrington (522) observed chromatolytic changes specially in the postero-external group of cells of the anterior horn of the spinal cord after section of the posterior roots, and attributed them to withdrawal of the afferent impulses which normally impinge on the cornual cells. K. Schaffer (466) found similar alterations of this group of nerve-cells in a case of cerebral hemiplegia of short duration, and regarded them as consecutive to degeneration of the pyramidal tract. Lugaro (257a) believes that these cells are sensory neurons of the second order, and thinks that their degeneration in Schaffer's case may perhaps be explained by injury to their ascending prolongations in the brain. It must not, however, be inferred from this that Lugaro denies the occurrence of degeneration by transmission.

In concluding this digest, I desire to express my indebtedness especially to Dr. Clouston, Dr. Alexander Bruce, Dr. D. A. Welsh, Dr. W. R. Dawson and Dr. Harry Rainy for the kind assistance they have given me in getting access to literature.

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Review.

The Medical Jurisprudence of Insanity or Forensic Psychiatry. 2 vols., 8vo, pp. 1356, 1898. The Lawyers' Co-operative Publishing Company. Rochester, New York.

THIS ambitious work is, as the author tells us in his preface, an attempt to unite a general medical text-book upon insanity with a medico-legal treatise and a digest of the English and American law to meet the requirements of lawyers and physicians in civil and criminal cases.

The scope of the work is very wide. It comprises definitions, classification, symptoms and diagnosis as the medical part of the first volume, followed by reports of criminal cases, legal adjudications in criminal cases, civil cases and legal adjudications in them, and an important chapter upon evidence of insanity, concluding with a chapter on the competency of witnesses and jurors.

The second volume treats of alcoholism, the legal consequences of it, and the decisions of the Courts upon it, together with a chapter on Morphinism, and other addictions and many other subjects, among which we may mention Degeneracy, Hysteria, Epilepsy, &c., and concludes with chapters on Etiology, Prognosis, Pathology, and treatment. As will be seen by this rapid survey, the work covers an enormous amount of ground. The author handles his subject in a clear and comprehensive manner, and has succeeded in giving to the profession as the result of his great labour a valuable and reliable medico-legal treatise upon what he terms "Forensic Psychiatry."

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